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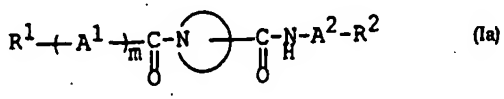

(Ia)

(57) Abstract

This invention relates to β-alanine derivatives represented by formula (Ia) wherein each symbol is as defined in the specification and pharmaceutically acceptable salt thereof which is glycoprotein IIB/IIIa antagonist, inhibitor of blood platelets aggregation and inhibitor of the binding of fibrinogen to blood platelets, to processes for the preparation thereof, to a pharmaceutical composition comprising the same and to a method for the prevention and/or treatment diseases indicated in the specification to a human being or an animal.

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DESCRIPTION

N-Acylpiperidinylcarbonylaminocarboxylic acids and their use as glycoprotein IIB/IIIa antagonists and fibrinogen - blood platelets binding inhibitors

TECHNICAL FIELD

The present invention relates to β-alanine derivative and a pharmaceutically acceptable salt thereof. More particularly, it relates to β-alanine derivative and a salt thereof which is glycoprotein IIb/IIIa antagonist, inhibitor of blood platelets aggregation and inhibitor of the binding of fibrinogen to blood platelets.

BACKGROUND ART

In European Patent Application No. 512,831 A1, there are disclosed fibrinogen receptor antagonists.

In European Patent Application No. 445,796 A2, there are disclosed inhibitor of blood platelets aggregation.

DISCLOSURE OF INVENTION

The present invention relates to β-alanine derivative and a salt thereof. More particularly, it relates to β-alanine derivative and a salt thereof which is glycoprotein IIb/IIIa antagonist and inhibitor of platelet aggregation, and useful as :

a drug for the prevention and/or the treatment of diseases caused by thrombus formation such as arterial thrombosis; arterial sclerosis; ischemic heart diseases [e.g. angina pectoris (e.g. stable angina pectoris, unstable angina pectoris including imminent infarction, etc.), myocardial infarction (e.g. acute myocardial infarction, etc.), coronary thrombosis, etc.]; ischemic brain diseases [e.g. cerebral infarction (e.g. cerebral thrombosis (e.g. acute cerebral thrombosis, etc.), cerebral embolism, etc.), transient cerebral ischemia (e.g. transient ischemic attack, etc.), cerebrovascular

spasm after cerebral hemorrhage (e.g. cerebrovascular spasm after subarachnoid hemorrhage, etc.), etc.]; pulmonary vascular diseases (e.g. pulmonary thrombosis, pulmonary embolism etc.); peripheral circulatory disorder [e.g. arteriosclerosis obliterans, thromboangiitis obliterans (i.e. Bürger's disease), Raynaud's disease, complication of diabetes mellitus (e.g. diabetic angiopathy, diabetic neuropathy, etc.), phlebothrombosis (e.g. deep vein thrombosis, etc.), etc.] or the like;

a drug for the prevention and/or the treatment of restenosis and/or reocclusion such as restenosis and/or reocclusion after percutaneous transluminal coronary angioplasty (PTCA), restenosis and/or reocclusion after the administration of thrombolytic drug (e.g. tissue plasminogen activator (TPA), etc.) or the like;

a drug for the adjuvant therapy with thrombolytic drug (e.g. TPA, etc.) or anticoagulant (e.g. heparin, etc.);

a drug for the prevention and/or the treatment of the thrombus formation in case of vascular surgery, valve replacement, extracorporeal circulation [e.g. surgery (e.g. open heart surgery, pump-oxygenator, etc.) hemodialysis, etc.], transplantation, or the like;

a drug for the prevention and/or the treatment of disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia, essential thrombocytosis, inflammation (e.g. nephritis, etc.), immune diseases, or the like;

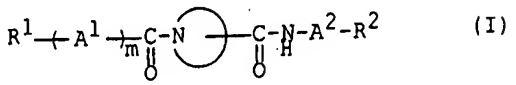
a drug for inhibiting of metastasis; or the like.

The β-alanine derivative of the present invention is expected to be useful as an inhibitor of cell adhesion and so is expected to be useful as

a drug for the prevention and/or the treatment of disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia, essential thrombocytosis, inflammation

(e.g. nephritis, etc.), immune diseases, or the like;
a drug for inhibiting of metastasis; or the like.

The object β-alanine derivative of the present invention can be shown by the following formula (I) :



(I)

wherein R^1 is piperidyl, piperidyl having amino protective group, tetrahydropyridyl, tetrahydropyridyl having amino protective group, azetidinyl, azetidinyl having amino protective group, tetrahydroisoquinolyl or tetrahydroisoquinolyl having amino protective group,

R^2 is carboxy or protected carboxy,

A^1 is lower alkylene, lower alkanyl-ylidene, lower alkenylene, cyclo(lower)alkylene or arylene,

A^2 is lower alkylene which may have one or more suitable substituent(s) or arylene,

 is piperidinediyl or

tetrahydroisoquinolinediyl, and

m is an integer of 0 or 1,

with proviso that

when R^1 is piperidyl,

A^1 is lower alkylene, and

A^2 is lower alkylene which may have one or more suitable substituent(s) except 5 or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), which may have one or more lower alkyl;
ar(lower)alkoxy(lower)alkyl;
hydroxy(lower)alkyl;
lower alkoxy(lower)alkyl;
cyclo(lower)alkyl;
aroylamino(lower)alkyl;
lower alkanoylamino(lower)alkyl which may have halogen;
lower alkanoylamino having halogen;
and aroylamino having
halo(lower)alkyl;

then R^2 is pentyloxycarbonyl,
isopentyloxycarbonyl,
isohexyloxycarbonyl,
phenethyloxycarbonyl, aryloxycarbonyl
or indanyloxycarbonyl,

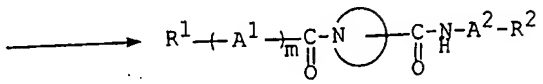
or a salt thereof.

The object compound (I) or a salt thereof can be prepared by the following processes.

Process 1

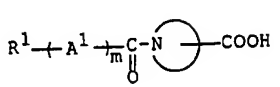
(II)
or its reactive derivative at the carboxy group or a salt thereof

(III)
or its reactive derivative at the amino group or a salt thereof



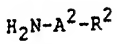
(I)
or a salt thereof

Process 2

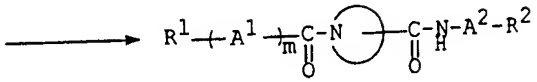


(IV)
or its reactive derivative
at the carboxy group
or a salt thereof

+

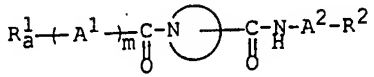


(V)
or its reactive derivative
at the amino group
or a salt thereof



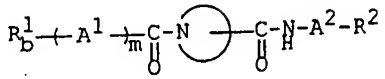
(I)
or a salt thereof

Process 3



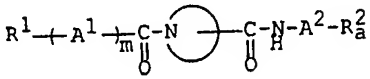
elimination reaction
of amino protective
group

(Ia)
or a salt thereof



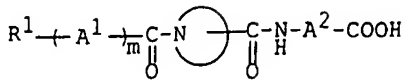
(Ib)
or a salt thereof

Process 4



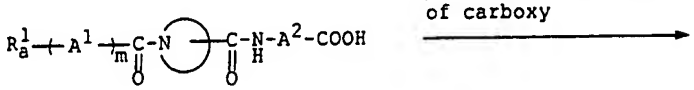
elimination reaction
of carboxy protective
group

(Ic)
or a salt thereof

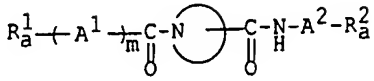


(Id)
or a salt thereof

Process 5



(Ie)
or its reactive derivative
at the carboxy group
or a salt thereof



(If)
or a salt thereof

wherein R^1, R^2, A^1, A^2, and m are each as defined above,

R_a^1 is piperidyl having amino protective group, tetrahydropyridyl having amino protective group, azetidinyl having amino protective group or tetrahydroisoquinolyl having amino protective group,

R_b^1 is piperidyl, tetrahydropyridyl, azetidinyl or tetrahydroisoquinolyl,

R_a^2 is protected carboxy, and

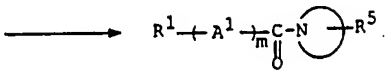
 is piperidyl or tetrahydroisoquinolyl.

The starting compound (IV) or a salt thereof is novel and can be prepared by the following schemes.

Process A

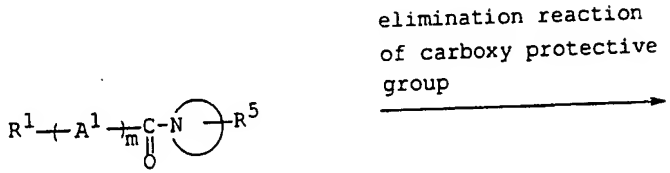
(II)
or its reactive derivative
at the carboxy group
or a salt thereof

(VI)
or its reactive derivative
at the amino group
or a salt thereof

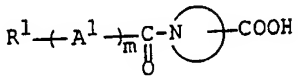


(VII)
or a salt thereof

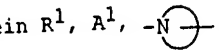
Process B



(VII)
or a salt thereof



(IV)
or a salt thereof

wherein R^1, A^1,  and m are each as defined above,

R^5 is protected carboxy, and

 is piperidyl or tetrahydroisoquinolyl.

Among the starting compounds (II), (III), (V), (VI) and (VII), there are novel compounds. They can be prepared from the known compounds in a conventional manner in this field of the art or the similar manners to those disclosed in Preparations and/or Examples mentioned later

in the present specification.

Suitable salts of the object compound (I) are pharmaceutically acceptable salts such as conventional non-toxic salts and include a metal salt such as an alkali metal salt [e.g. sodium salt, potassium salt, etc.] and an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.] an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt dicyclohexylamine salt, N,N-dibenzylethylenediamine salt, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, etc.], a salt with an amino acid [e.g. arginine salt, aspartic acid salt, glutamic acid salt, etc.] and the like.

In the above and subsequent descriptions of this specification, suitable examples of the various definitions are explained in detail as follows :

The term "lower" is intended to mean 1 to 6 carbon atom(s), unless otherwise indicated.

The term "higher" is used to intend a group having 7 to 20 carbon atoms, unless otherwise provided.

The preferable number of the "one or more" in the term "one or more suitable substituent(s)" may be 1 to 3.

Suitable "lower alkyl" may be straight or branched ones such as methyl, ethyl, isopropyl, propyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, hexyl, isohexyl or the like.

Suitable "protected carboxy" may be carboxy protected

by a conventional protecting group such as an esterified carboxy group, or the like, and concrete examples of the ester moiety in said esterified carboxy group may be the ones such as lower alkyl ester [e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, isopentyl ester, hexyl ester, isohexyl ester, 1-cyclopropylethyl ester, etc.] which may have suitable substituent(s), for example, lower alkanoyloxy(lower)alkyl ester [e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, 1-acetoxyethyl ester, 1-propionyloxyethyl ester, pivaloyloxyethyl ester, 2-propionyloxyethyl ester, hexanoyloxymethyl ester, etc.], lower-alkanesulfonyl(lower)alkyl ester [e.g. 2-mesylethyl ester, etc.] or mono(or di or tri)halo(lower)alkyl ester [e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.];

higher alkyl ester [e.g. heptyl ester, octyl ester, 3,5-dimethyloctyl ester, 3,7-dimethyloctyl ester, nonyl ester, decyl ester, undecyl ester, dodecyl ester, tridecyl ester, tetradecyl ester, pentadecyl ester, hexadecyl ester, heptadecyl ester, octadecyl ester, nonadecyl ester, adamantyl ester, etc.];

lower alkenyl ester [e.g. (C_2-C_6)alkenyl ester (e.g. vinyl ester, allyl ester, etc.)];

lower alkynyl ester [e.g. (C_2-C_6)alkynyl ester (e.g. ethynyl ester, propynyl ester, etc.)];

ar(lower)alkyl ester which may have one or more suitable substituent(s) [e.g. phenyl(lower)alkyl ester which may have 1 to 4 lower alkoxy, halogen, nitro, hydroxy, lower alkyl, phenyl, or halo(lower)alkyl, (e.g. benzyl ester, 4-methoxybenzyl ester, 4-chlorobenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester,

4-hydroxy-3,5-di-tert-butylbenzyl ester, 4-trifluoromethylbenzyl ester, etc.)];

aryl ester which may have one or more suitable substituent(s) [e.g. phenyl ester which may have 1 to 4 lower alkyl, or halogen, (e.g. phenyl ester, 4-chlorophenyl ester, tolyl ester, 4-tert-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, etc.), indanyl ester, etc.];

cycloalkyloxycarbonyloxy(lower)alkyl ester which may have lower alkyl (e.g., cyclopentyloxycarbonyloxymethyl ester, cyclohexyloxycarbonyloxymethyl ester, cycloheptyloxycarbonyloxymethyl ester, 1-methylcyclohexyloxycarbonyloxymethyl ester, 1-(or 2-)-[cyclopentyloxycarbonyloxy]ethyl ester, 1-(or 2-)-[cyclohexyloxycarbonyloxy]ethyl ester, 1-(or 2-)-[cycloheptyloxycarbonyloxy]ethyl ester, etc.), etc.];

(5-(lower)alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester [e.g., (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)methyl ester, 1-(or 2-)(5-methyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, 1-(or 2-)(5-ethyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, 1-(or 2-)(5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.]; or the like,

in which the preferred one may be lower alkyl ester, ar(lower)alkyl ester, aryl ester which may have one or more suitable substituent(s) cycloalkyloxycarbonyloxy-(lower)alkyl ester or lower alkanoyloxy(lower)alkyl ester,

and the more preferred one may be methyl ester, ethyl ester, butyl ester, pentyl ester, isopentyl ester, isohexyl ester, phenethyl ester, phenyl ester, indanyl ester, pivaloyloxymethyl ester or 1-cyclohexyloxycarbonyloxyethyl ester.

Suitable "lower alkanyl-ylidene" may include straight or branched one such as methine, 1-ethanyl-2-ylidene,

1-propanyl-3-ylidene, 2-methyl-1-propanyl-3-ylidene, 7-pentanyl-5-ylidene, 1-hexanyl-6-ylidene and the like.

Suitable "lower alkylene" may include straight or branched one such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, methylmethylene, 1-ethylethylene, 2-ethylpropylene, and the like, in which the preferred one may be (C_1-C_4)-alkylene, and the more preferred one may be ethylene and propylene.

Suitable "lower alkenylene" may include straight or branched one having 2 to 6 carbon atom(s) such as vinylene, 1 or 2-propenylene, 1 or 2 or 3-butenylene, 1 or 2 or 3-pentenylene, 1 or 2 or 3-hexenylene, 1 or 2-methylvinylene, 1 or 2-ethylvinylene, 1 or 2 or 3-methylpropenylene, 1 or 2 or 3-ethylpropenylene, 1 or 2 or 3 or 4-methyl-1 or 2-butenylene, or the like, in which the preferred one may be (C_2-C_4)alkenylene, and the more preferred one may be vinylene, 1-propenylene, 1-methylvinylene and 2-methylvinylene.

Suitable "cyclo(lower)alkylene" may be cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene or the like, in which the preferred one may be cyclo(C_3-C_6)alkylene, and the most preferred one may be cyclopropylene.

Suitable "arylene" may be phenylene, naphthylene, anthrylene or the like, in which the preferred one may be 1,2-phenylene, 1,3-phenylene and 1,4-phenylene.

Suitable "amino protective group" may include acyl group as explained below, a conventional protecting group such as ar(lower)alkyl which may have 1 to 3 suitable substituent(s) (e.g. benzyl, phenethyl, 1-phenylethyl, benzhydryl, trityl, etc.), [5-(lower)alkyl-2-oxo-1,3-

dioxol-4-yl](lower)alkyl [e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl, etc.] or the like; and the like.

Suitable "acyl group" and "acyl" may include aliphatic acyl, aromatic acyl, arylaliphatic acyl and heterocyclic-aliphatic acyl derived from carboxylic acid, carbonic acid, carbamic acid, sulfonic acid, and the like.

Suitable example of said "acyl group" may be illustrated as follows :

aliphatic acyl such as lower or higher alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.);
lower or higher alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.);
lower or higher alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.);
lower or higher alkoxysulfonyl (e.g., methoxysulfonyl, ethoxysulfonyl, etc.); or the like;

aromatic acyl such as
aroyl (e.g., benzoyl, toluoyl, naphthoyl, etc.);
ar(lower)alkanoyl [e.g., phenyl(C_1-C_6)alkanoyl (e.g., phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(C_1-C_6)alkanoyl (e.g., naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc), etc.];
ar(lower)alkenoyl [e.g., phenyl(C_3-C_6)alkenoyl (e.g., phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, etc.), naphthyl(C_3-C_6)-

alkenoyl (e.g., naphthylpropenoyl, naphthylbutenoyl, etc.), etc.];

ar(lower)alkoxycarbonyl (e.g., phenyl(C_1-C_6)-alkoxycarbonyl (e.g., benzyloxycarbonyl, etc.), etc.];

aryloxycarbonyl (e.g., phenoxycarbonyl, naphthyloxycarbonyl, etc.);

aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.);

arylcarbamoyl (e.g., phenylcarbamoyl, etc.);

arylthiocarbamoyl (e.g., phenylthiocarbamoyl, etc.);

arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl, etc.);

arylsulfonyl which may have 1 to 4 lower alkyl (e.g., phenylsulfonyl, p-tolylsulfonyl, etc.); or the like;

heterocyclic acyl such as

heterocycliccarbonyl;

heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl, heterocyclicpropanoyl, heterocyclicbutanoyl, heterocyclicpentanoyl, heterocyclichexanoyl, etc.);

heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl, heterocyclichexenoyl, etc.);

heterocyclicglyoxyloyl; or the like; and the like.

Suitable "heterocyclic moiety" in the terms "heterocycliccarbonyl", "heterocyclic(lower)alkyl", "heterocyclic(lower)alkenoyl" and "heterocyclicglyoxyloyl" as mentioned above, and "heterocyclic group" mean saturated or unsaturated monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an oxygen, sulfur, nitrogen atom and the like, in which the preferable heterocyclic group may be heterocyclic group such as

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl,

imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, dihydroquinolyl, isoquinolyl, indazolyl, quinoxalinyl, dihydroquinoxalinyl, benzotriazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2

sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.;

unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like.

The acyl moiety as mentioned above may have one to ten, same or different, suitable substituent(s) such as lower alkyl (e.g., methyl, ethyl, propyl, etc.);
lower alkoxy (e.g., methoxy, ethoxy, propoxy, etc.);
lower alkylthio (e.g., methylthio, ethylthio, etc.);
lower alkylamino (e.g., methylamino, ethylamino, propylamino, etc.);
cyclo(lower)alkyl [e.g. cyclo(C_3-C_6)alkyl (e.g., cyclopentyl, cyclohexyl, etc.)];
cyclo(lower)alkenyl [e.g. cyclo(C_3-C_6)alkenyl (e.g., cyclohexenyl, cyclohexadienyl, etc);
halogen (e.g., fluorine, chlorine, bromine, iodine);

amino; amino protective group as mentioned above; hydroxy; protected hydroxy as mentioned below; cyano; nitro; carboxy; protected carboxy as mentioned above; sulfo; sulfamoyl; imino; oxo;
amino(lower)alkyl (e.g., aminomethyl, aminoethyl, etc.); carbamoyloxy; hydroxy(lower)alkyl (e.g., hydroxymethyl, 1 or 2-hydroxyethyl, 1 or 2 or 3-hydroxypropyl, etc.), or the like.

Suitable "protected hydroxy" may include acyl as mentioned above, phenyl(lower)alkyl which may have one or more suitable substituent(s) (e.g., benzyl, 4-methoxybenzyl, trityl, etc.), trisubstituted silyl [e.g., tri(lower)alkylsilyl (e.g., trimethylsilyl, t-butyldimethylsilyl, etc.), etc.], tetrahydropyranyl and the like.

The more preferred example of "amino protective group" may be lower alkoxycarbonyl or ar(lower)alkoxycarbonyl and the most preferred one may be t-butoxycarbonyl or benzyloxycarbonyl.

Suitable "lower alkylene" in the term "lower alkylene which may have one or more suitable substituent(s)" can be referred to the ones as exemplified above.

Suitable example of "suitable substituent(s)" in the term "lower alkylene which may have one or more suitable substituent(s)" may include lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, neopentyl, t-pentyl, hexyl, etc.);
lower alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, t-butoxy, pentyloxy, neopentyloxy, t-pentyloxy, hexyloxy, etc.);
lower alkenyl [e.g. (C_2-C_6)alkenyl (e.g., vinyl, 1-propenyl, allyl, 1-methylallyl, 1 or 2 or 3-butenyl, 1 or 2 or 3 or 4-pentenyl, 1 or 2 or 3 or 4 or 5-hexenyl,

etc.)];

lower alkynyl [e.g. (C_2-C_6)alkynyl (e.g., ethynyl, 1-propynyl, propargyl, 1-methylpropargyl, 1-ethylpropargyl, 1 or 2 or 3-butynyl, 1 or 2 or 3 or 4-pentynyl, 1 or 2 or 3 or 4 or 5 hexynyl, etc.);

mono(or di or tri)halo(lower)alkyl (e.g., fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, 1 or 2-fluoroethyl, 1 or 2-bromoethyl, 1 or 2-chloroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, etc.);

halogen (e.g., chlorine, bromine, fluorine, iodine);

carboxy; protected carboxy as mentioned above; hydroxy; protected hydroxy as mentioned above;

aryl (e.g., phenyl, naphthyl, etc.);

heterocyclic group as mentioned above [e.g. unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.),

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.), in which said heteromonocyclic group as mentioned above may have one or more, same or different, suitable substituent(s) such as lower alkyl (e.g., methyl, ethyl, propyl, etc.), lower alkoxy (e.g., methoxy, ethoxy, propoxy, etc.), or the like];

ar(lower)alkyl such as phenyl(lower)alkyl (e.g., benzyl, phenethyl, phenylpropyl, etc.);

ar(lower)alkyl having one or more suitable substituent(s) such as ar(lower)alkyl having one or more (preferably 1 to 4) lower alkoxy, halogen, cyano, halo(lower)alkyl, lower alkylene dioxy or the like;

carboxy(lower)alkyl; protected carboxy(lower)alkyl;

nitro; amino;

protected amino, i.e. amino protected by aforesaid "amino protective group", preferably, acylamino, in which acyl moiety can be aforementioned "acyl", such as aliphatic acylamino such as lower or higher alkanoylamino which may have one or more suitable substituent(s) (e.g., formylamino, acetylamino, trifluoroacetylamino, propanoylamino, butanoylamino, 2-methylpropanoylamino, pentanoylamino, 2,2-dimethylpropanoylamino, hexanoylamino, heptanoylamino, octanoylamino, nonanoylamino, decanoylamino, undecanoylamino, dodecanoylamino, tridecanoylamino, tetradecanoylamino, pentadecanoylamino, hexadecanoylamino, heptadecanoylamino, octadecanoylamino, nonadecanoylamino, icosanoylamino, etc.),

cyclo(lower)alkylcarbonylamino [e.g. cyclo(C_3-C_6)-alkylcarbonylamino (e.g. cyclopropylcarbonylamino, cyclobutylcarbonylamino, cyclopentylcarbonylamino, cyclohexylcarbonylamino, etc.)], lower or higher alkoxycarbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, pentyloxycarbonylamino, heptyloxycarbonylamino, etc.),

lower alkoxy(lower)alkanoylamino (e.g. methoxyacetylamino, 2- or 3-methoxypropionylamino, ethoxyacetylamino, 2- or 3-ethoxypropionylamino, etc.),

lower alkynylcarbonylamino [e.g. (C_2-C_6)-alkynylcarbonylamino (e.g. propargylcarbonylamino, 1-methylpropargylcarbonylamino, 1- or 2- or 3-butynylcarbonylamino, etc.),

lower or higher alkylsulfonylamino (e.g., methylsulfonylamino, ethylsulfonylamino,

propylsulfonylamino, n-butylsulfonylamino, sec-butylsulfonylamino, t-butylsulfonylamino, n-pentylsulfonylamino, neo-pentylsulfonylamino, hexylsulfonylamino, etc.),

lower or higher alkoxysulfonylamino (e.g., methoxysulfonylamino, ethoxysulfonylamino, etc.),

aroylamino which may have one or more (preferably 1 to 3) suitable substituent(s) (e.g. benzoylamino, toluoylamino, naphthoylamino, 2- or 3- or 4-hydroxybenzoylamino, 2- or 3- or 4-methoxybenzoylamino, 2- or 3- or 4-chlorobenzoylamino, 2- or 3- or 4-trifluorobenzoylamino, phenylbenzoylamino, etc.),

ar(lower)alkanoylamino [e.g., phenyl(C_1-C_6)alkanoylamino (e.g., phenylacetylamino, phenylpropanoylamino, phenylbutanoylamino, phenylisobutanoylamino, phenylpentanoylamino, phenylhexanoylamino, etc.), naphthyl(lower)alkanoylamino (e.g., naphthylacetylamino, naphthylpropanoylamino, naphthylbutanoylamino, etc.), etc.],

ar(lower)alkenoylamino [e.g., phenyl(C_3-C_6)alkenoylamino (e.g., phenylpropenoylamino, phenylbutenoylamino, phenylmethacryloylamino, phenylpentenoylamino, phenylhexenoylamino, etc.), naphthyl(C_3-C_6)alkenoylamino (e.g., naphthylpropenoylamino, naphthylbutenoylamino, etc.), etc.],

ar(lower)alkoxycarbonylamino [e.g., phenyl(C_1-C_6)alkoxy-carbonylamino (e.g. benzyloxycarbonylamino, phenethyloxycarbonylamino, etc.), etc.],

aryloxycarbonylamino (e.g., phenoxycarbonylamino, naphthyloxycarbonylamino, etc.),

aryloxy(lower)alkanoylamino (e.g., phenoxyacetylamino, phenoxypropionylamino, etc.),

arylcarbamoylamino (e.g., phenylcarbamoylamino, etc.),

arylthiocarbamoylamino (e.g., phenylthiocarbamoylamino, etc.),

arylglyoxyloylamino (e.g., phenylglyoxyloylamino, naphthylglyoxyloylamino, etc.),

arylsulfonylamino (e.g. phenylsulfonylamino, p-tolylsulfonylamino, etc.), or the like;

di(lower)alkylamino (e.g., dimethylamino, diethylamino, diisopropylamino, ethylmethylamino, isopropylmethylamino, ethylmethylamino, ethylpropylamino, etc.);

hydroxy(lower)alkyl; protected hydroxy(lower)alkyl; acyl as mentioned above; cyano; mercapto; oxo;

lower alkylthio(lower)alkyl (e.g. methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, methylthioethyl, ethylthioethyl, etc.);

arylthio(lower)alkyl (e.g. phenylthiomethyl, phenylthioethyl, etc.);

arylsulfonyl(lower)alkyl (e.g. phenylsulfonylmethyl, phenylsulfonylethyl, p-tolylsulfonylmethyl, p-tolylsulfonylethyl, etc.);

lower alkylsulfonyl(lower)alkyl (e.g. methylsulfonylmethyl, ethylsulfonylmethyl, propylsulfonylmethyl, etc.);

acylamino(lower)alkyl which may have one or more suitable substituent(s), in which acyl moiety can be aforementioned "acyl" [e.g., arylsulfonylamino(lower)alkyl (e.g., phenylsulfonylaminomethyl, phenylsulfonylaminoethyl, p-tolylsulfonylaminomethyl, p-tolylsulfonylethyl, etc.), lower alkylsulfonylamino(lower)alkyl (e.g., methylsulfonylaminomethyl, ethylsulfonylaminomethyl, propylsulfonylaminomethyl, butylsulfonylaminomethyl, t-butylsulfonylaminomethyl, pentylsulfonylaminoethyl, etc.), lower alkanoylamino(lower)alkyl which may have one or more suitable substituent(s) (e.g., acetylaminomethyl, acetylaminoethyl, trifluoroacetylaminomethyl, trifluoroacetylaminoethyl, etc.), aroylamino(lower)alkyl (e.g., benzoylaminomethyl, benzoylaminoethyl, naphthoylaminomethyl, etc.), etc.];

lower alkylcarbonyl(lower)alkyl (e.g. methylcarbonylmethyl, ethylcarbonylmethyl, propylcarbonylmethyl, etc.);

aroyl(lower)alkyl (e.g. benzoylmethyl, naphthoylmethyl, toluoylmethyl, anisoylmethyl, etc.);

heterocyclic(lower)alkyl such as (lower)alkyl having heterocyclic group as exemplified above [e.g. (C_1-C_6)alkyl having unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s) (e.g. indolylethyl, isoindolylethyl, indolyinylmethyl, indolizinylethyl, benzimidazolylmethyl, quinolylethyl, dihydroquinolylmethyl, isoquinolylethyl, indazolylethyl, quinoxalinylethyl, dihydroquinoxalinylmethyl, benzotriazolylethyl, etc.)];

lower alkyl sulfamoyl(lower)alkyl (e.g. methylsulfamoylmethyl, ethylsulfamoylmethyl, n-propylsulfamoylmethyl, isopropylsulfamoylmethyl, n-butylsulfamoylmethyl, t-butylsulfamoylmethyl, methylsulfamoylethyl, etc.);

arylsulfamoyl(lower)alkyl (e.g. phenylsulfamoylmethyl, tolylsulfamoylmethyl, phenylsulfamoylethyl, naphthylsulfamoylmethyl, etc.);

lower alkylcarbamoyl(lower)alkyl (e.g. methylcarbamoylmethyl, ethylcarbamoylmethyl, n-propylcarbamoylmethyl, isopropylcarbamoylmethyl, n-butylcarbamoylmethyl, t-butylcarbamoylmethyl, methylcarbamoylethyl, etc.);

arylcarbamoyl(lower)alkyl (e.g. phenylcarbamoylmethyl, tolylcarbamoylmethyl, phenylcarbamoylethyl, naphthylcarbamoylmethyl, etc.);

ar(lower)alkylcarbamoyl which may have one or more suitable substituent(s) [e.g. phenyl(C_1-C_6)alkylcarbamoyl which may have 1 to 3 lower alkoxy (e.g. 2-methoxyphenethylcarbamoyl, 3-methoxyphenethylcarbamoyl, 4-methoxyphenethylcarbamoyl, etc.);

lower alkoxy(lower)alkyl (e.g., methoxymethyl, methoxyethyl, ethoxymethyl, ethoxyethyl, propoxymethyl, propoxyethyl, butoxybutyl, pentyloxymethyl, hexyloxyethyl, etc.);

cyclo(lower)alkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.);

ar(lower)alkoxy(lower)alkyl (e.g., benzyloxymethyl, benzyloxyethyl, benzyloxypropyl, benzyloxybutyl, benzyloxypentyl, benzyloxyhexyl, phenethyloxymethyl, phenethyloxyethyl, etc.) and the like,

in which the more preferred "suitable substituent(s)" in the term "lower alkylene which may have one or more suitable substituent(s)" may be (C_1-C_6)alkyl; (C_2-C_6)-alkynyl; phenyl; phenyl(C_1-C_6)alkyl; (C_1-C_6)alkanoylamino; aroylamino; 5 or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have lower alkyl;

5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s);

phenyl(C_1-C_6)alkyl having 1 or 2 (C_1-C_6)alkoxy;

(C_1-C_6)alkoxy(C_1-C_6)alkyl;

cyclo(C_1-C_6)alkyl; hydroxy(C_1-C_6)alkyl;

phenyl(C_1-C_6)alkoxy(C_1-C_6)alkyl;

(C_1-C_6)alkanoylamino(C_1-C_6)alkyl having 1 to 3 halogen;

aroylamino having 1 to 3 halo(lower)alkyl;

(C_1-C_6)alkanoylamino having 1 to 3 halo(lower)alkyl;

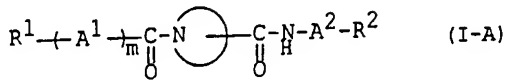
aroylamino having (C_1-C_6)alkoxy;

aroylamino(C_1-C_6)alkyl; or (C_1-C_6)alkanoylamino(C_1-C_6)-alkyl;

and the most preferred one may be methyl, ethynyl, phenyl, phenethyl, acetylamino, benzoylamino, 3- or 4- or 5-methyl isoxazolyl, triazolyl, 4-methoxyphenethyl, 3,4-dimethoxyphenethyl, methoxymethyl, cyclopropyl, hydroxymethyl, benzyloxymethyl, trifluoroacetylaminomethyl, trifluorobenzoylamino,

trifluoroacetylamino, methoxybenzoylamino, benzoylaminomethyl or acetylaminomethyl.

In the compound (I) as explained above, the preferred one is the following compound (I-A) :



(I-A)

wherein

R^1 is piperidyl, piperidyl having amino protective group, tetrahydropyridyl, tetrahydropyridyl having amino protective group, azetidinyl, azetidinyl having amino protective group, tetrahydroisoquinolyl, or tetrahydroisoquinolyl having amino protective group,

R^2 is carboxy or protected carboxy,

A^1 is lower alkenylene,

A^2 is lower alkylene,

lower alkylene which may have 1 to 3 suitable substituent(s) selected from the group consisting of lower alkyl, lower alkynyl, aryl, ar(lower)alkyl which may have 1 to 3 lower alkoxy, lower alkanoylamino which may have 1 to 3 halogen, aroylamino which may have 1 to 3 halo(lower)alkyl, heterocyclic group which may have 1 to 3 lower alkyl, lower alkoxy(lower)alkyl, cyclo(lower)alkyl, hydroxy(lower)alkyl, ar(lower)alkoxy(lower)alkyl and lower alkanoylamino(lower)alkyl which may have 1 to 3 halogen or arylene,

 is piperidinediyl or tetrahydroisoquinolinediyl,

and

m is an integer of 1,

and the more preferred one is the aforementioned compound

(I-A), wherein

R^1 is piperidyl, piperidyl having amino protective group, tetrahydropyridyl, tetrahydropyridyl having amino protective group, azetidinyl, azetidinyl having amino protective group, tetrahydroisoquinolyl or tetrahydroisoquinolyl having amino protective group,

R^2 is carboxy or protected carboxy,

A^1 is lower alkenylene,

A^2 is lower alkylene,

lower alkylene which has one suitable substituent selected from the group consisting of lower alkyl, lower alkynyl, aryl, ar(lower)alkyl which may have 1 or 2 lower alkoxy, lower alkanoylamino which may have 3 halogens, aroylamino which may have one tri-halo(lower)alkyl, 5 or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) which may have one lower alkyl, 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), lower alkoxy(lower)alkyl, cyclo(lower)alkyl, hydroxy(lower)alkyl, ar(lower)alkoxy(lower)alkyl and lower alkanoylamino(lower)alkyl which may have 3 halogens or phenylene,

 is piperidinediyl or tetrahydroisoquinolinediyl

and

m is an integer of 1,

and the much more preferred one is the aforementioned compound (I-A), wherein

R^1 is piperidyl or tetrahydropyridyl,

R^2 is carboxy or protected carboxy,

A^1 is lower alkenylene,

A^2 is lower alkylene or lower alkylene which has one suitable substituent selected from the group consisting of lower alkyl, lower alkynyl, phenyl, phenyl(lower)alkyl which may have 1 or 2 lower

alkoxy, lower alkanoylamino, benzoylamino which may have one tri-halo(lower)alkyl, isoxazolyl which has one lower alkyl, triazolyl and phenyl(lower)alkoxy(lower)alkyl,

 is piperidinediyl, and

m is an integer of 1,

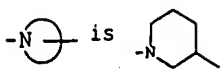
and the most preferred one is the aforementioned compound (I-A), wherein

R^1 is 4-piperidyl or 4-tetrahydropyridyl,

R^2 is carboxy or protected carboxy,

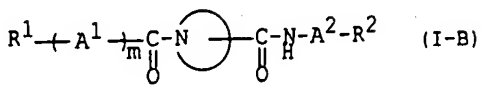
A^1 is vinylene,

A^2 is lower alkylene or lower alkylene which has one substituent selected from the group consisting of methyl, ethynyl, phenyl, phenethyl, acetylamino, benzoylamino, isoxazolyl having methyl, triazolyl, methoxyphenethyl, dimethoxyphenethyl, benzyloxymethyl and trifluorobenzoylamino,

 is , and

m is an integer of 1.

In the compound (I) as explained above, another preferred one is the following compound (I-B) :

 (I-B)

wherein

R^1 is piperidyl,

R^2 is pentyloxycarbonyl, isopentyloxycarbonyl, isohexyloxycarbonyl, phenethyloxycarbonyl, phenyloxycarbonyl or indanyloxycarbonyl,

A^1 is lower alkylene,

A^2 is lower alkylene which has one substituent selected from the group consisting of lower alkynyl and lower alkanoylamino,

 is piperidinediyl, and

m is an integer of 1,

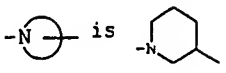
and the much more preferred one is the aforementioned compound (I-B), wherein

R^1 is 4-piperidyl,

R^2 is pentyloxycarbonyl, isopentyloxycarbonyl, isohexyloxycarbonyl, phenethyloxycarbonyl, phenyloxycarbonyl or indanyloxycarbonyl,

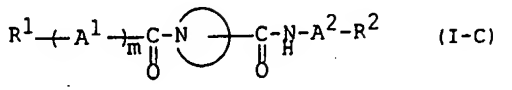
A^1 is ethylene,

A^2 is lower alkylene which has one substituent selected from the group consisting of ethynyl and acetylamino,

 is , and

m is an integer of 1.

In the compound (I) as explained above, another preferred one is the following compound (I-C) :

 (I-C)

wherein

R^1 is piperidyl or piperidyl having amino protective group,

R^2 is carboxy or protected carboxy,

A^1 is lower alkylene,

A^2 is lower alkylene which has one substituent selected from the group consisting of 5 or 6-membered

heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) having lower alkyl, phenyl(lower)alkoxy(lower)alkyl, hydroxy(lower)alkyl, lower alkoxy(lower)alkyl, cyclo(lower)alkyl, benzoylamino(lower)alkyl, lower alkanoylamino(lower)alkyl, tri-halo(lower)-alkanoylamino, benzoylamino having tri-halo(lower)-alkyl and tri-halo(lower)alkanoylamino(lower)alkyl or arylene,

 is piperidinediyl, and

m is an integer of 1,

and the more preferred one is the aforementioned compound (I-C), wherein

R^1 is piperidyl,

R^2 is carboxy,

A^1 is lower alkylene,

A^2 is lower alkylene which has one substituent selected from the group consisting of isoxazolyl having lower alkyl, tri-halo(lower)alkylbenzoylamino, benzoylamino(lower)alkyl, tri-halo(lower)alkanoylamino(lower)alkyl,

 is piperidinediyl, and

m is an integer of 1,

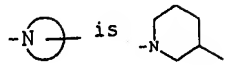
and the most preferred one is the aforementioned compound (I-C), wherein

R^1 is 4-piperidyl,

R^2 is carboxy,

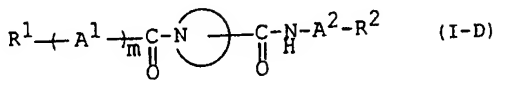
A^1 is lower alkylene,

A^2 is lower alkylene which has one substituent selected from the group consisting of isoxazolyl having methyl, trifluorobenzoylamino, benzoylaminomethyl and trifluoroacetylaminomethyl,

 is , and

m is an integer of 1.

In the compound (I) as explained above, another preferred one is the following compound (I-D) :

 (I-D)

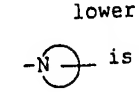
wherein

R^1 is tetrahydropyridyl or tetrahydropyridyl having amino protective group,

R^2 is carboxy or protected carboxy,

A^1 is lower alkylene,

A^2 is lower alkylene which has one substituent selected from the group consisting of lower alkynyl and 5 or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) having lower alkyl,

 is piperidinediyl, and

m is an integer of 1,

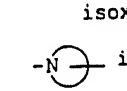
and the more preferred one is the aforementioned compound (I-D), wherein

R^1 is tetrahydropyridyl,

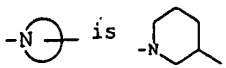
R^2 is carboxy,

A^1 is lower alkylene,

A^2 is lower alkylene which has one substituent selected from the group consisting of lower alkynyl and isoxazolyl having lower alkyl,

 is piperidinediyl, and

m is an integer of 1,
and the most preferred one is the aforementioned compound (I-D), wherein
R^1 is 4-tetrahydropyridyl,
R^2 is carboxy,
A^1 is lower alkylene,
A^2 is lower alkylene which has one substituent selected from the group consisting of ethynyl and isoxazolyl having methyl,

 is , and

m is an integer of 1.

The processes for preparing the object compound (I) of the present invention are explained in detail in the following.

Process 1

The object compound (I) or a salt thereof can be prepared by reacting a compound (II) or its reactive derivative at the carboxy group or a salt thereof with a compound (III) or its reactive derivative at the amino group or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound (II) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic

carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole, tetrazole or 1-hydroxy-1H-benzotriazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=C-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivative can optionally be selected from them according to the kind of the compound (II) to be used.

Suitable salts of the compound (II) and its reactive derivative can be referred to the ones as exemplified for the compound (I).

Suitable reactive derivative at the amino group of the compound (III) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (III) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (III) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (III) with phosphorus trichloride or phosgene, and the

like.

Suitable salts of the compound (III) and its reactive derivative can be referred to the ones as exemplified for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (II) in used in a free acid form or its salt form, the reaction is preferable carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkylphosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorous oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, methanesulfonyl chloride, etc.;

or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal carbonate, alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 2

The object compound (I) or a salt thereof can be prepared by reacting a compound (IV) or its reactive derivative at the carboxy group or a salt thereof with a compound (V) or its reactive derivative at the amino group or a salt thereof.

This reaction can be carried out in a similar manner to that of Process 1 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. reactive derivative, solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

Process 3

The object compound (Ib) or a salt thereof can be prepared by subjecting a compound (Ia) or a salt thereof to elimination reaction of amino protective group.

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate

thereof, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.].

The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal

platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium, sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

The present invention includes within the scope of the invention the case that protected carboxy in R^2 is transformed into carboxy.

Process 4

The object compound (Id) or a salt thereof can be prepared by subjecting a compound (Ic) or a salt thereof to elimination reaction of the carboxy protective group.

This reaction can be carried out in a similar manner to that of Process 3 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. base, acid, catalyst, solvent, reaction temperature, etc.] of

this reaction are to be referred to those as explained in Process 3.

Process 5

The object compound (If) or a salt thereof can be prepared by subjecting the compound (Ie) or a salt thereof to protecting reaction of carboxy.

This reaction can be carried out according to a conventional manner such as the ones described in Examples or the similar manners thereto.

The processes for preparing the starting compound (IV) is explained in detail in the following.

Process A

The object compound (VII) or a salt thereof can be prepared by reacting a compound (II) or its reactive derivative at the carboxy group or a salt thereof with a compound (VI) or its reactive derivative at the amino group or a salt thereof.

This reaction can be carried out in a similar manner to that of Process 1 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. reactive derivative, solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

Process B

The object compound (IV) or a salt thereof can be prepared by subjecting a compound (VII) or a salt thereof to elimination reaction of the carboxy protective group.

This reaction can be carried out in a similar manner to that of Process 3 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. base, acid, catalyst, solvent, reaction temperature, etc.] of

this reaction are to be referred to those as explained in Process 3.

The present invention includes within the scope of the invention the case that amino protective group in R^1 is transformed into amino.

When the object compound (I) obtained by the above-mentioned processes is in a free form, it can be converted into a salt form in a conventional manner. On the other hand, when the object compound (I) thus obtained is in a salt form, it can be converted into a free form or another salt form also in a conventional manner.

The compounds obtained by the above Processes 1 to 5 and A to B can be isolated and purified by a conventional method such as pulverization, recrystallization, column-chromatography, reprecipitation or the like.

It is to be noted that each of the object compound (I) may include one or more stereoisomer such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s) and all such isomers and mixture thereof are included within the scope of this invention.

The object compound (I) or a pharmaceutically acceptable salt thereof include solvated compound [e.g., enclosure compound (e.g., hydrate, etc.)].

The object compound (I) or a pharmaceutically acceptable salt thereof include both its crystal form and non-crystal form.

Now in order to show the utility of the object compound (I), some pharmacological test data of the representative compound (I) of the present invention are shown in the following.

Test 1 : Effect on platelet aggregation induced by adenosine diphosphate (ADP)

Test Compound

(1) the compound of Example 25

Test Method

Platelet rich plasma (PRP) which contains 3×10^8 platelets/ml was prepared from human blood. To the 225 µl of PRP, 25 µl of drug solution* was added, and then stirred for 2 minutes at 37°C. To the solution 5 µl of ADP (final 2.5 µM) was added as an aggregation inducer. Aggregation was measured by using an aggregometer (NBS HEMA-TRACER 801). Activity of inhibitor (test compound) was expressed as IC_{50} value i.e. dose required for complete inhibition of platelet aggregation.

Drug solution* --- Test compound was dissolved in water.

Test Result

Test Compound	IC_{50} (µM)
(1)	0.085

The pharmaceutical composition of the present invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the object compound (I) or a pharmaceutically acceptable salt thereof, as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administrations or insufflation.

The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, troches, capsules, suppositories, creams, ointments, aerosols, powders for insufflation, solutions, emulsions, suspensions, and any other form suitable for use. And, if necessary, in addition, auxiliary, stabilizing, thickening and coloring agents and perfumes may be used.

The object compound (I) or a pharmaceutically acceptable salt thereof is/are included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the diseases.

The pharmaceutical composition of the present invention can be manufactured by the conventional method in this field of the art. If necessary, the technique generally used in this field of the art for improving the bioavailability of a drug can be applied to the pharmaceutical composition of the present invention.

For applying the composition to a human being or an animal, it is preferable to apply it by intravenous (including i.v. infusion), intramuscular, pulmonary, or oral administration, or insufflation including aerosols from metered dose inhalator, nebulizer or dry powder inhalator.

While the dosage of therapeutically effective amount of the object compound (I) varies from and also depends upon the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.001-100 mg of the object compound (I) per kg weight of a human being or an animal, in the case of

intramuscular administration, a daily dose of 0.001-100 mg of the object compound (I) per kg weight of a human being or an animal, in case of oral administration, a daily dose of 0.001-200 mg of the object compound (I) per kg weight of a human being or an animal in generally given for the prevention and/or the treatment of aforesaid diseases in a human being or an animal.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

To a solution of ethyl 3 azido-2(S)-aminopropionate hydrochloride (0.3 g) in dichloromethane (3 ml) was added triethylamine (0.47 ml) and benzoyl chloride (0.2 ml) under stirring at 0°C. After stirring at ambient temperature for 2 hours, the mixture was poured into water and extracted with dichloromethane. The extract was washed with water, saturated aq. $NaHCO_3$, water and brine, and dried over magnesium sulfate, and evaporated in vacuo. The residue was recrystallized from diethyl ether to give ethyl 3 azido-2(S)-(benzoylamino)propionate (0.35 g).

mp : 56°C

IR (Nujol) : 3260, 2090, 1730, 1640 cm^{-1}

NMR ($CDCl_3$, δ) : 1.34 (3H, t, J=7.1Hz), 3.88 (2H, qd, J=9.0 and 3.3Hz), 4.32 (2H, d, J=7.1Hz), 4.91-4.98 (1H, m), 6.96-7.04 (1H, m), 7.42-7.59 (3H, m), 7.81-7.86 (2H, m)

MASS (m/z) : 263 (M^++1)

Preparation 2

A mixture of ethyl 3-azido-2(S)-(benzoylamino)-propionate (0.35 g) and 10% Pd-C (0.07 g) in ethanol (4 ml) was hydrogenated at an atmospheric pressure for 2 hours. After the catalyst was removed by filtration, the

filtrate was concentrated in vacuo to give ethyl 3-amino-2(S)-(benzoylamino)propionate (0.25 g).

mp : 59°C

IR (Nujol) : 3320, 1730, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 1.19 (3H, t, J=7.0Hz), 2.93-2.97 (2H, m), 4.11 (2H, q, J=7.1Hz), 4.36-4.45 (1H, m), 7.44-7.56 (3H, m), 7.87-7.92 (2H, m), 8.59 (1H, d, J=7.0Hz)

MASS (m/z) : 237 (M^++1)

Preparation 3

tert-butyldimethylsilyl chloride (1.42 g) was added to a mixture of 4(S)-ethynyl-2-azetidinone (0.78 g) in dichloromethane (10 ml) and ethyldiisopropylamine (2.14 ml) at room temperature. The reaction mixture was stirred overnight, then evaporated in vacuo. The residue was purified by column chromatography on silica gel eluting with n-hexane - ethyl acetate (9:1) to give 1-tert-butyldimethylsilyl-4(S)-ethynyl-2-azetidinone (1.4 g) as a colorless oil.

IR (Nujol) : 3280, 1730 cm^{-1}

NMR ($CDCl_3$, δ) : 0.28 (3H, s), 0.29 (3H, s), 0.98 (9H, s), 2.45 (1H, d, J=2.0Hz), 3.10 (3H, dd, J=3.0 and 15.1Hz), 3.40 (3H, dd, J=5.7 and 15.1Hz), 4.10-4.15 (1H, m)

MASS (m/z) : 210 (M^++1)

Preparation 4

A solution of phenylisocyanate (0.93 ml) in benzene (5 ml) was added to a mixture of 1-tert-butyldimethylsilyl-4(S)-ethynyl-2-azetidinone (1.0 g) in benzene (10 ml), nitroethane (0.35 ml), and triethylamine (0.1 ml) in benzene (5 ml) at room temperature. The reaction mixture was refluxed for 8 hours, then evaporated in vacuo. The residue was purified by column

chromatography on silica gel eluting with n-hexane - ethyl acetate (9:1) to give 1-tert-butyldimethylsilyl-4(S)-(3-methyl-5-isoxazolyl)-2-azetidinone (0.96 g) as a colorless oil.

IR (Film) : 3120, 1740, 1605 cm^{-1}

NMR ($CDCl_3$, δ) : 0.05 (3H, s), 0.77 (3H, s), 0.91 (9H, s), 2.31 (3H, s), 3.22 (3H, dd, J=3.0 and 15.3Hz), 3.51 (3H, dd, J=5.8 and 15.3Hz), 4.66 (3H, dd, J=3.0 and 5.8Hz), 6.11 (1H, s)

MASS (m/z) : 267 (M^++1)

Preparation 5

A solution of 1-tert-butyldimethylsilyl-4(S)-(3-methyl-5-isoxazolyl)-2-azetidinone (0.9 g) in EtOH (10 ml) was added HCl (16.9 mmol)/EtOH (4.2 ml) at room temperature at 0°C. The reaction mixture was stirred at room temperature for 2 hours, then evaporated in vacuo. The residue was recrystallized from diethyl ether to give 3(S)-(3-methyl-5-isoxazolyl)-β-alanine ethyl ester hydrochloride (0.67 g) as a white solid.

IR (Nujol) : 3400, 2000, 1715, 1605 cm^{-1}

NMR (DMSO-d_6, δ) : 1.61 (3H, t, J=7.2Hz), 2.25 (3H, s), 3.03-2.98 (2H, m), 4.08 (2H, d, J=7.2Hz), 4.80-4.88 (1H, m), 6.60 (1H, s), 9.14 (2H, br)

MASS (m/z) : 199 (M^+ free+1)

Preparation 6

To a mixture of ethyl (R)-nipecotinate (1.86 g), 3-[1-(tert-butoxycarbonyl)-4-piperidyl]-(E)-acrylic acid (3.2 g) and 1-hydroxybenzotriazole (1.60 g) in dimethylformamide (20 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (2.16 ml) at 0°C. The reaction mixture was stirred overnight at room temperature, and then poured into water. The whole was extracted with ethyl acetate, washed with aqueous

saturated $NaHCO_3$, water, and brine, dried over $MgSO_4$, and evaporated in vacuo, subsequently. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$-MeOH (99:1) to give ethyl (R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidinecarboxylate as a colorless oil (4.46 g).

IR (Film) : 3450, 2940, 2860, 1725, 1680, 1620 cm^{-1}

NMR ($CDCl_3$, δ) : 1.27 (3H, t, J=7.1Hz), 1.26-1.46 (2H, m), 1.46 (9H, s), 1.52-1.82 (8H, m), 2.02-2.14 (1H, m), 2.21-2.36 (1H, m), 2.44-2.56 (1H, m), 2.69-2.83 (2H, m), 3.02-3.10 (1H, m), 4.08-4.17 (2H, m), 4.15 (2H, q, J=7.1Hz), 6.27 (1H, d, J=15.1Hz), 6.81 (1H, dd, J=6.7 and 15.1Hz)

Preparation 7

A solution of LiOH (0.32 g) in H_2O (20 ml) was added to a solution of ethyl (R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidinecarboxylate (4.46 g) in tetrahydrofuran (20 ml)-EtOH (20 ml) at 0°C. The reaction mixture was stirred for 3 hours at the same condition, and the solvent was evaporated in vacuo. The residue was resolved in ethyl acetate - water, and acidified with 10% aq. $KHSO_4$. The whole was washed with water, brine, dried over $MgSO_4$, and evaporated in vacuo, subsequently. The residue was recrystallized from diethyl ether to give (R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidinecarboxylic acid as a white solid (3.07 g).

mp : 128-129°C

IR (Film) : 1720, 1680, 1660 cm^{-1}

NMR (DMSO-d_6, δ) : 1.08-1.31 (2H, m), 1.39 (9H, s), 1.65-1.70 (5H, m), 1.84-1.99 (1H, m), 2.24-2.41 (2H, m), 2.74-2.82 (2H, m), 3.04 (1H, m), 3.32-3.46 (2H, m), 3.85-3.98 (3H, m), 6.43 (1H, d, J=15.8Hz), 6.60 (1H, d, J=5.4 and 15.8Hz), 12.4

(1H, s)

MASS (m/z) : 367 (M^++1)

Preparation 8

A mixture of 1-tert-butyldimethylsilyl-4(S)-ethynyl-2-azetidinone (3.0 g) and trimethylsilylazide (15 ml) was heated at 80°C for 20 hours. The reaction mixture was allowed to room temperature and evaporated in vacuo. The residue was purified by column chromatography on silica gel eluting with n-hexane ethyl acetate = (1:1) to give 1-tert-butyldimethylsilyl-4(S)-(2H-1,2,3-triazol-4-yl)-2-azetidinone (0.3 g, 8.3%) as a pale yellow solid.

IR (Nujol) : 3180, 3050, 1710 cm^{-1}

NMR ($CDCl_3$, δ) : 0.35 (3H, s), 0.19 (3H, s), 0.85 (9H, s), 3.20 (1H, dd, J=2.9 and 15.5Hz), 3.58 (1H, dd, J=5.7 and 15.5Hz), 4.86 (1H, dd, J=2.9 and 5.7Hz), 7.75 (1H, s)

MASS (m/z) : 253 (M^+)

Preparation 9

1-tert-Butyldimethylsilyl-4(S)-(2H-1,2,3-triazol-4-yl)-2-azetidinone (0.3 g) was added to 6N HCl/EtOH (10 ml). The mixture was stirred for 1 hour, and then evaporated in vacuo. The crystalline solid was washed with diethyl ether to give 3(S)-(2H-1,2,3-triazol-4-yl)-β-alanine ethyl ester hydrochloride (0.25 g, 94.4%) as a white solid.

NMR ($CDCl_3$, δ) : 1.04 (3H, t, J=7.1Hz), 3.11 (2H, d, J=7.0Hz), 4.97 (1H, t, J=7.0Hz), 7.93 (1H, s)

MASS (m/z) : 184 (M^++1)

Preparation 10

To a solution of trimethylsulfoxonium iodide (1.16 g, 5.25 mmol) in dimethylsulfoxide (10 ml) was added sodium hydride (60% dispersion in oil, 210 mg, 5.25 mmol) under 0°C, and the solution was stirred at room temperature for 10 minutes. To the resulting mixture was added a solution of 3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acrylic acid

methyl ester (1.37 g, 5.09 mmol) was added dropwise under 0°C, and it was stirred for 1 hour at room temperature and for 2 hours at 50°C. After cooling to 0°C, saturated aqueous ammonium chloride was added to quench the reaction. The mixture was extracted with diethyl ether (50 ml x 2), and the organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was purified by column chromatography (n-hexane/ethyl acetate = 7/1) to give 2-(1-tert-butoxycarbonyl-4-piperidyl)-(1R*,2S*)-cyclopropane-1-carboxylic acid methyl ester.

IR (Neat) : 1730, 1690 cm^{-1}

NMR ($CDCl_3$, δ) : 0.70-1.00 (2H, m), 1.10-1.50 (5H, m), 1.45 (9H, s), 1.60-2.00 (2H, m), 2.50-2.75 (2H, m), 3.66 (3H, s), 3.90-4.20 (2H, m)

MASS (m/z) : 184 (M^++1-Boc)

The following compounds [Preparations 11 to 21] were obtained according to a similar manner to that of Preparation 6.

Preparation 11

Ethyl (R)-1-[3-(1-tert-butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridyl)-(E)-acryloyl]-3-piperidinecarboxylate

IR (Film) : 1730, 1690, 1640, 1620, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.26 (3H, t, J=7.1Hz), 1.47 (9H, s), 1.66-1.78 (2H, m), 2.02-2.17 (2H, m), 2.30 (2H, br), 2.42-2.56 (1H, br), 2.85-3.18 (2H, br), 3.54-3.59 (2H, m), 3.84-3.95 (2H, br), 4.07 (2H, br), 4.15 (2H, d, J=7.1Hz), 6.01 (1H, br), 6.21-6.45 (1H, m), 7.28 (1H, d, J=15.0Hz)

Preparation 12

Ethyl (R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-

(Z)-acryloyl]-3-piperidinecarboxylate

IR (Film) : 1720, 1690, 1630, 1615 cm^{-1}

NMR ($CDCl_3$, δ) : 1.17-1.38 (2H, m), 1.26 (3H, t, J=7.2Hz), 1.46 (9H, s), 1.65-1.77 (4H, m), 2.04-2.11 (1H, m), 2.42-2.52 (1H, m), 2.70-3.45 (5H, m), 3.76-3.91 (1H, m), 4.04-4.60 (5H, m), 3.94-4.24 (2H, m), 5.64-5.77 (1H, m), 5.96, 6.04 (total 1H, d, J=11.6Hz)

Preparation 13

Ethyl (S)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidinecarboxylate

IR (Film) : 2910, 1850, 1720, 1680, 1650, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.26 (3H, t, J=7.1Hz), 1.30-1.63 (3H, m), 1.46 (9H, s), 1.69-1.88 (4H, m), 2.03-2.14 (1H, m), 2.21-2.39 (1H, m), 2.42-2.54 (1H, m), 2.70-2.82 (2H, m), 3.03-3.14 (1H, m), 3.35-3.54 (1H, m), 3.83-3.95 (1H, m), 4.08-4.75 (5H, m), 6.30 (1H, d, J=15.2Hz), 6.81 (1H, dd, J=15.2 and 6.7Hz)

MASS (m/z) : 395 (M^++1)

Preparation 14

Ethyl (R)-1-[3-(1-tert-butoxycarbonyl-3-azetidinyl)-(E)-acryloyl]-3-piperidinecarboxylate

IR (Neat) : 1700 cm^{-1}

NMR ($CDCl_3$, δ) : 1.26 (3H, t, J=7.1Hz), 1.43 (9H, s), 1.50-2.20 (4H, m), 2.20-3.20 (3H, m), 3.20-3.60 (1H, m), 3.65-4.05 (5H, m), 4.05-4.25 (3H, m), 4.40-4.75 (1H, br), 6.20-6.45 (1H, m), 6.98 (1H, dd, J=15.0 and 8.2Hz)

MASS (m/z) : 367 (M^++1)

Preparation 15

Ethyl (R)-1-[4-(1-tert-butoxycarbonyl-3-azetidinyl)-

(E)-2-butenoyl]-3-piperidinecarboxylate

IR (Neat) : 1690, 1650, 1620 cm^{-1}

NMR ($CDCl_3$, δ) : 1.27 (3H, t, J=7.1Hz), 1.44 (9H, s), 1.45-1.95 (5H, m), 1.95-2.20 (1H, m), 2.35-2.75 (3H, m), 3.00-3.25 (1H, m), 3.35-4.25 (8H, m), 6.20-6.40 (1H, m), 6.67-6.82 (1H, m)

MASS (m/z) : 381 (M^++1)

Preparation 16

Ethyl (R)-1-[(2-tert-butoxycarbonyl-1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]-3-piperidinecarboxylate

IR (Nujol) : 1720, 1690, 1630 cm^{-1}

NMR ($CDCl_3$, δ) : 1.20-1.30 (3H, m), 1.49 (9H, m), 1.60-1.90 (3H, m), 2.05-2.20 (1H, m), 2.35-2.70 (1H, m), 2.75-2.95 (2H, m), 2.95-3.45 (4H, m), 3.65 (2H, t, J=5.9Hz), 4.05-4.25 (2H, m), 4.58 (2H, s), 7.10-7.27 (3H, m)

MASS (m/z) : 417 (M^++1)

Preparation 17

Ethyl (R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-methacryloyl]-3-piperidinecarboxylate

Preparation 18

Ethyl (R)-1-[2-[1-tert-butoxycarbonyl-4-piperidyl]-(1R*,2S*)-cyclopropan-1-yl-carbonyl]-3-piperidinecarboxylate

IR (Neat) : 1730, 1680, 1630 cm^{-1}

NMR ($CDCl_3$, δ) : 0.55-1.05 (2H, m), 1.05-1.35 (7H, m), 1.46 (9H, s), 1.50-1.95 (4H, m), 1.95-2.35 (1H, m), 2.35-3.65 (6H, m), 3.90-4.35 (6H, m), 4.45-4.85 (1H, m)

MASS (m/z) : 409 (M^++1)

Preparation 19

Ethyl (R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-3-methyl-(E)-acryloyl]-3-piperidinecarboxylate

IR (Neat) : 1730, 1690, 1630 cm^{-1}

NMR ($CDCl_3$, δ) : 1.25-1.60 (2H, m), 1.26 (3H, t, J=7.1Hz), 1.46 (9H, s), 1.60-1.80 (4H, m), 1.83 (3H, s), 1.90-2.20 (3H, m), 2.30-2.55 (1H, m), 2.70 (2H, t, J=11.9Hz), 2.80-3.40 (2H, m), 3.60-3.95 (1H, m), 4.00-4.35 (4H, m), 4.45-4.75 (1H, m), 5.78 (1H, d, J=13.6Hz)

MASS (m/z) : 409 (M^++1)

Preparation 20

Ethyl (R)-1-[4-(1-tert-butoxycarbonyl-3-piperidyl)-2-butenoyl]-3-piperidinecarboxylate

IR (Neat) : 1730, 1680 cm^{-1}

NMR ($CDCl_3$, δ) : 0.95-3.30 (16H, m), 1.45 (9H, s), 3.30-4.25 (8H, m), 4.50-4.80 (1H, m), 6.15-6.45 (1H, m), 6.75-6.90 (1H, m)

MASS (m/z) : 409 (M^++1)

Preparation 21

Ethyl (R)-1-[3-(1-tert-butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridyl)propanoyl]-3-piperidinecarboxylate

IR (Film) : 1730, 1690, 1640 cm^{-1}

NMR ($CDCl_3$, δ) : 1.15-1.31 (3H, t, J=7.0Hz), 1.46 (9H, s), 1.67-1.77 (3H, m), 2.04-2.07 (3H, m), 2.33-2.50 (5H, m), 2.98-3.11 (2H, m), 3.36-3.51 (2H, m), 3.76-3.85 (3H, m), 4.02-4.21 (3H, m), 5.38 (1H, br)

The following compounds [Preparation 22 to 33] were obtained according to a similar manner to that of Preparation 7.

Preparation 22

(R)-1-[3-(1-tert-Butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridyl)-(E)-acryloyl]-3-piperidinecarboxylic acid

IR (Film) : 1730, 1690, 1640, 1620, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.47 (9H, s), 1.78 (2H, br), 2.09 (1H, br), 2.29 (2H, br), 2.55 (1H, br), 3.20 (2H, br), 3.54-3.60 (2H, m), 3.95 (2H, br), 4.07-4.11 (2H, m), 6.01 (1H, br), 6.28 (1H, br), 7.28 (1H, d, J=15.0Hz)

Preparation 23

(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(Z)-acryloyl]-3-piperidinecarboxylic acid

Preparation 24

(S)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidinecarboxylic acid

IR (Nujol) : 1705, 1680, 1660 cm^{-1}

NMR (DMSO-d_6, δ) : 1.08-1.31 (2H, m), 1.39 (9H, s), 1.39-1.74 (6H, m), 1.89-2.01 (1H, m), 2.24-2.44 (1H, m), 2.70-2.89 (2H, m), 2.97-3.12 (1H, m), 3.29-3.48 (1H, m), 3.80-4.01, 4.36-4.49 (total 4H, m), 6.43 (1H, d, J=15.5Hz), 6.60 (1H, dd, J=15.5 and 5.5Hz), 12.39 (1H, br)

MASS (m/z) : 367 (M^++1)

Preparation 25

(R)-1-[3-(1-tert-Butoxycarbonyl-3-azetidinyl)-(E)-acryloyl]-3-piperidinecarboxylic acid

IR (Neat) : 1700 cm^{-1}

NMR ($CDCl_3$, δ) : 1.43 (9H, s), 1.45-2.20 (3H, m), 2.20-2.85 (3H, m), 2.85-3.50 (2H, m), 3.60-4.20 (6H, m), 5.40-6.10 (1H, br), 6.20-6.50 (1H, m), 6.80-7.10 (1H, m)

Preparation 26

(R)-1-[4-(1-tert-Butoxycarbonyl-3-azetidinyl)-(E)-2-butenoyl]-3-piperidinecarboxylic acid

IR (Neat) : 1710, 1690 cm^{-1}

NMR ($CDCl_3$, δ) : 1.44 (9H, s), 1.45-2.20 (3H, m), 2.40-2.80 (4H, m), 2.90-3.95 (8H, m), 4.03 (2H, t, J=8.5Hz), 6.15-6.50 (1H, m), 6.70-6.84 (1H, m)

MASS (m/z) : 353 (M^++1)

Preparation 27

(R)-1-[(2-tert-Butoxycarbonyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)carbonyl]-3-piperidinecarboxylic acid

NMR ($CDCl_3$, δ) : 1.35-1.90 (5H, m), 1.49 (9H, s), 2.00-2.25 (1H, m), 2.35-2.70 (1H, m), 2.84 (2H, t, J=5.8Hz), 2.95-3.40 (2H, m), 3.65 (2H, t, J=5.8Hz), 4.58 (2H, s), 5.10-5.80 (1H, br), 7.00-7.25 (3H, m)

MASS (m/z) : 389 (M^++1)

Preparation 28

(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-methacryloyl]-3-piperidinecarboxylic acid

NMR ($CDCl_3$, δ) : 1.15-1.45 (2H, m), 1.46 (9H, s), 1.50-1.95 (6H, m), 1.86 (3H, d, J=2.2Hz), 2.00-2.10 (1H, m), 2.30-2.65 (2H, m), 2.65-2.95 (2H, m), 2.95-3.35 (2H, m), 3.80-4.25 (3H, m), 4.90-5.80 (1H, br), 5.34 (1H, d, J=7.7Hz)

MASS (m/z) : 281 (M^++1-Boc)

Preparation 29

2-(1-tert-Butoxycarbonyl-4-piperidyl)-(1R*,2S*)-cyclopropane-1-carboxylic acid

IR (Neat) : 1680 cm^{-1}

NMR ($CDCl_3$, δ) : 0.75-1.00 (2H, m), 1.15-1.60 (5H, m), 1.46 (9H, s), 1.60-1.80 (2H, m), 2.50-2.75

(2H, m), 3.90-4.25 (2H, m)
MASS (m/z) : 170 (M^++1-Boc)

Preparation 30

(R)-1-[2-(1-tert-Butoxycarbonyl-4-piperidyl)-(1R*,2S*)-cyclopropan-1-yl-carbonyl-3-piperidinecarboxylic acid

IR (Neat) : 1670 cm^{-1}

NMR ($CDCl_3$, δ) : 0.60-2.35 (11H, m), 1.45 (9H, s), 2.35-4.25 (10H, m), 6.15-7.20 (1H, br)

MASS (m/z) : 381 (M^++1)

Preparation 31

(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-3-methyl-(E)-acryloyl]-3-piperidinecarboxylic acid

IR (Neat) : 1730, 1690 cm^{-1}

NMR ($CDCl_3$, δ) : 1.25-1.60 (2H, m), 1.46 (9H, s), 1.60-1.95 (4H, m), 1.83 (3H, s), 1.95-2.20 (2H, m), 2.35-2.60 (1H, m), 2.60-2.80 (2H, m), 2.90-3.25 (2H, m), 3.25-3.55 (1H, m), 3.65-4.35 (3H, m), 4.40-4.65 (1H, m), 5.78 (1H, d, J=13.9Hz), 5.85-6.70 (1H, br)

MASS (m/z) : 381 (M^++1)

Preparation 32

(R)-1-[4-(1-tert-Butoxycarbonyl-3-piperidyl)-2-butenoyl]-3-piperidinecarboxylic acid

NMR ($CDCl_3$, δ) : 1.00-4.20 (21H, m), 1.45 (9H, s), 6.20-6.40 (1H, m), 6.65-6.88 (1H, m)

MASS (m/z) : 381 (M^++1)

Preparation 33

(R)-1-[3-(1-tert-Butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridyl)propanoyl]-3-piperidinecarboxylic acid

IR (Film) : 1720, 1690 cm^{-1}

The following compound was obtained according to a similar manner to that of Preparation 6.

Preparation 34

Methyl 2-[3-[1-(tert-butoxycarbonyl)-4-piperidyl]-(E)-acryloyl]-1,2,3,4-tetrahydroisoquinoline-4-carboxylate

NMR ($CDCl_3$, δ) : 1.30-1.50 (2H, m), 1.46 (9H, s), 1.65-1.85 (2H, m), 2.20-2.50 (1H, m), 2.78 (2H, t-like), 3.50-4.00 (2H, m), 3.70 (3H, s), 4.00-4.30 (2H, m), 4.40-4.65 (2H, m), 5.00-5.25 (1H, m), 6.25-6.60 (1H, m), 6.88 (1H, dd, J=15.3 and 6.6Hz), 7.10-7.40 (4H, m)

MASS (m/z) : 429 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 7.

Preparation 35

2-[3-[1-(tert-Butoxycarbonyl)-4-piperidyl]-(E)-acryloyl]-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid

Example 1

To a mixture of (R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidinecarboxylic acid (1 g), 3(S)-ethynyl-β-alanine ethyl ester hydrochloride (0.48 g) and 1-hydroxybenzotriazole (0.37 g) in dimethylformamide (10 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.5 ml) at 0°C. The reaction mixture was stirred overnight at room temperature, and then poured into water. The whole was extracted with ethyl acetate, washed with aqueous saturated $NaHCO_3$, water, and brine, dried over $MgSO_4$, and evaporated in vacuo, subsequently. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$-MeOH (99:1) to give N-[(R)-1-[3-(1-tert-

butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester as a pale yellow oil (1.34 g).

IR (Film) : 3250, 2910, 2850, 1720, 1650, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.28 (3H, t, J=7.1Hz), 1.25-1.57 (2H, m), 1.46 (9H, s), 1.70-1.80 (3H, m), 1.92-2.10 (2H, m), 2.24-2.40 (2H, m), 2.28 (1H, d, J=2.3Hz), 2.70-2.85 (4H, m), 3.22-3.41 (2H, m), 3.65-3.80 (1H, m), 4.07-4.25 (4H, m), 4.18 (2H, q, J=7.1Hz), 5.05-5.17 (1H, m), 6.22 (1H, d, J=15.1Hz), 6.83 (1H, dd, J=7.1 and 15.1Hz), 7.02-7.18 (1H, m)

MASS (m/z) : 490 (M^++1)

The following compounds [Examples 2 to 7] were obtained according to a similar manner to that of Example 1.

Example 2

N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)propionyl]-3-piperidylcarbonyl]-3(S)-(3-methyl-5-isoxazolyl)-β-alanine ethyl ester

IR (Film) : 3360, 1730, 1640 cm^{-1}

NMR ($CDCl_3$, δ) : 1.09-1.25 (3H, m), 1.26 (3H, t, J=7.2Hz), 1.45 (9H, s), 1.53-1.71 (6H, m), 1.91-1.95 (2H, m), 2.26 (3H, s), 2.39-2.46 (3H, m), 2.61-2.72 (2H, m), 2.87-2.93 (1H, m), 3.10 (1H, br), 3.36-3.50 (2H, m), 3.78 (1H, br), 3.96-4.07 (3H, m), 4.12 (2H, d, J=7.2Hz), 5.57-5.78 (1H, m), 5.99 (1H, s)

MASS (m/z) : 549 (M^+ free+1)

Example 3

N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3-phenyl-β-alanine methyl ester

IR (Film) : 3000, 2930, 2860, 1740, 1670, 1650, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.24-1.56 (5H, m), 1.46 (9H, s), 1.68-1.90 (4H, m), 2.03-2.51 (3H, m), 2.69-2.90 (4H, m), 3.40-3.60 (1H, m), 3.60, 3.63 (total 3H, s), 3.70-3.88 (1H, m), 4.06-4.20 (2H, m), 5.37-5.47 (1H, m), 6.15-6.28 (1H, m), 6.78 (1H, dd, J=15.2 and 6.5Hz), 7.26-7.51 (6H, m)

MASS (m/z) : 528 (M^++1)

Example 4

N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2(S)-(acetylamino)-β-alanine ethyl ester

IR (Film) : 2975, 2930, 2860 cm^{-1}

NMR ($CDCl_3$, δ) : 1.28 (3H, t, J=7.1Hz), 1.25-1.60 (6H, m), 1.46 (9H, s), 1.69-1.81 (2H, m), 2.07 (3H, s), 2.21-2.52 (3H, m), 2.70-2.84 (2H, m), 3.33-3.73 (4H, m), 3.95-4.27 (6H, m), 4.64-4.72 (1H, m), 6.27 (1H, d, J=15.3Hz), 6.82 (1H, dd, J=15.3 and 6.7Hz), 7.01-7.27 (1H, m)

MASS (m/z) : 523 (M^++1)

Example 5

N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(R)-methyl-β-alanine methyl ester

IR (Film) : 3060, 2970, 2930, 2850, 1725, 1645, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.22 (3H, t, J=6.8Hz), 1.28-1.60 (4H, m), 1.46 (9H, s), 1.68-1.80 (3H, m), 1.86-2.03 (2H, m), 2.23-2.40 (3H, m), 2.50 (2H, d, J=5.5Hz), 2.70-2.84 (2H, m), 3.32-3.56 (2H, m), 3.68 (3H, s), 4.00-4.19 (3H, m), 4.30-4.42 (1H,

m), 6.25 (1H, d, J=15.2Hz), 6.82 (1H, dd, J=6.7, and 15.2Hz)

MASS (m/z) : 466 (M^++1)

Example 6

N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(R)-phenethyl-β-alanine ethyl ester

IR (Film) : 2960, 2920, 2850, 1720, 1670, 1650 cm^{-1}

NMR ($CDCl_3$, δ) : 1.25 (3H, t, J=7.1Hz), 1.30-1.59 (2H, m), 1.46 (9H, s), 1.66-2.16 (8H, m), 2.22-2.40 (2H, m), 2.48-2.83 (6H, m), 3.24-3.68 (3H, m), 4.01-4.37 (6H, m), 6.23 (1H, d, J=15.2Hz), 6.81 (1H, dd, J=6.6 and 15.2Hz), 7.13-7.32 (6H, m)

MASS (m/z) : 570 (M^++1)

Example 7

N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2(S)-benzoylamino-β-alanine ethyl ester

IR (Film) : 2980, 2930, 2860, 1740, 1670, 1655, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.11-1.33 (2H, m), 1.30 (3H, t, J=7.1Hz), 1.46 (9H, s), 1.46-1.83 (6H, m), 2.09-2.55 (3H, m), 2.63-2.78 (2H, m), 3.26-3.72 (4H, m), 4.00-4.24 (5H, m), 4.82-4.90 (1H, m), 6.18 (1H, d, J=15.1Hz), 6.67 (1H, dd, J=6.3 and 15.1Hz), 7.33-7.65 (4H, m), 7.79-8.00 (3H, m)

MASS (m/z) : 585 (M^++1)

Example 8

A solution of LiOH (79 mg) in H_2O (10 ml) was added to a solution of N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-

ethynyl-β-alanine ethyl ester (1.34 g) in tetrahydrofuran (10 ml) - EtOH (10 ml) at 0°C. The reaction mixture was stirred for 3 hours at the same condition, and the solvent was evaporated in vacuo. The residue was resolved in ethyl acetate - water, and acidified with 10% aq. $KHSO_4$. The whole was washed with water, brine, dried over $MgSO_4$, and evaporated in vacuo to give N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine (1.23 g).

IR (Film) : 3270, 2920, 2850, 1720, 1650, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 1.12-1.35 (3H, m), 1.39 (9H, s), 1.50-1.80 (5H, m), 2.14-2.38 (2H, m), 2.56-3.20 (6H, m), 3.90-4.01 (4H,m), 4.17-4.38 (1H, m), 4.77-4.87 (1H, m), 6.42 (1H, d, J=15.1Hz), 6.60 (1H, dd, J=6.4 and 15.1Hz), 8.43 (1H, d, J=8.2Hz), 12.4 (1H, br)

MASS (m/z) : 462 (M^++1)

The following compounds [Examples 9 to 13] were obtained according to a similar manner to that of Example 8.

Example 9

N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2(S)-acetylamino-β-alanine

IR (Flim) : 2930, 1720, 1650 cm^{-1}

NMR (DMSO-d_6, δ) : 1.11-1.32 (3H, m), 1.39 (9H, m), 1.39-1.99 (7H, m), 1.91 (3H, m), 2.12-2.40 (1H, m), 2.51-2.86 (3H, m), 3.32-3.57 (2H, m), 3.89-4.06 (3H, m), 4.23-4.45 (2H, m), 6.39-6.67 (2H, m), 7.95-8.12 (2H, m)

MASS (m/z) : 495 (M^++1)

Example 10

N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-

acryloyl]-3-piperidylcarbonyl]-3(R)-methyl-β-alanine

IR (Film) : 2950, 2850, 1705, 1650, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 1.06 (3H, d, J=6.6Hz), 1.17-1.31 (2H, m), 1.39 (9H, s), 1.51-1.85 (5H, m), 2.07-2.40 (4H, m), 2.58-3.13 (5H, m), 3.91-4.40 (5H, m), 6.42 (1H, d, J=15.1Hz), 6.60 (1H, dd, J=6.4 and 15.1Hz), 7.83 (1H, d, J=7.9Hz), 12.10-12.20 (1H, br)

MASS (m/z) : 452 (M^++1)

Example 11

N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(R)-phenethyl-β-alanine

IR (Film) : 2920, 2850, 1710, 1645 cm^{-1}

NMR (DMSO-d_6,δ) : 1.11-1.32 (4H, m), 1.39 (9H, s), 1.60-1.89 (6H, m), 2.15-2.35 (2H, m), 2.38 (2H, d, J=6.8Hz), 2.55-3.21 (6H, m), 3.89-4.03 (4H, m), 4.20-4.40 (1H, m), 6.43 (1H, d, J=15.1Hz), 6.61 (1H, dd, J=6.3 and 15.1Hz), 7.15-7.30 (5H, m), 7.87 (1H, d, J=8.4Hz), 12.10 (1H, s)

MASS (m/z) : 542 (M^++1)

Example 12

N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2(S)-benzoylamino-β-alanine

IR (Film) : 2930, 1725, 1635, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 1.13-1.30 (2H, m), 1.39 (9H, s), 1.49-1.86 (6H, m), 2.16-2.36 (2H, m), 2.60-3.17 (4H, m), 3.38-3.69 (2H, m), 3.87-4.01 (3H, m), 4.19-4.59 (2H, m), 6.33-6.44 (1H, m), 6.59 (1H, dd, J=6.4 and 15.0Hz), 7.45-7.56 (3H, m), 7.83-7.87 (2H, m), 8.13-8.22 (1H, m), 8.58-8.64 (1H, m)

MASS (m/z) : 557 (M^++1)

Example 13

N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3-phenyl-β-alanine

IR (Film) : 3000, 2960, 2930, 2855, 1715, 1650 cm^{-1}

NMR (DMSO-d_6, δ) : 1.09-1.39 (2H, m), 1.39 (9H, s), 1.48-1.91 (6H, m), 2.14-2.37 (2H, m), 2.57-2.83 (6H, m), 3.87-4.01 (3H, m), 4.15-4.43 (1H, m), 5.18 (1H, q, J=7.6Hz), 6.34-6.66 (2H, m), 7.19-7.31 (5H, m), 8.41 (1H, d, J=8.4Hz), 12.17-12.26 (1H, br)

MASS (m/z) : 514 (M^++1)

Example 14

To a mixture of N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)propionyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine (0.5 g), 4-methyl-1-pentanol (0.15 ml) and N,N-dimethylaminopyridine (13 mg) in dichloromethane (5 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.23 g) at 0°C. After stirring at an ambient temperature overnight, the solution was evaporated in vacuo. The residue was poured into water and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate, water and brine, dried over magnesium sulfate, and evaporated in vacuo, subsequently. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$:MeOH (100:1) to give N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)propionyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine isohexyl ester (0.59 g) as an oil.

IR (Film) : 2930, 2860, 1735, 1680, 1630 cm^{-1}

NMR ($CDCl_3$, δ) : 0.89 (6H, d, J=6.6Hz), 0.97-1.29 (5H, m), 1.45 (9H, s), 1.50-2.15 (11H, m), 2.27 (1H, d, J=2.2Hz), 2.36 (3H, t, J=7.8Hz), 2.62-2.72 (5H, m), 3.29-3.40 (2H, m), 3.51 (1H, m), 4.10 (2H, t, J=6.8Hz), 4.03-4.20 (2H, m), 5.04-

5.16 (1H, m), 6.77 and 7.01 (total 1H, d, J=8.6Hz)

MASS (m/z) : 548 (M^++1)

The following compounds [Examples 15 to 18] were obtained according to a similar manner to that of Example 14.

Example 15

N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-propionyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine isopentyl ester

IR (Film) : 3000, 2940, 2860, 1730, 1660, 1620 cm^{-1}

NMR ($CDCl_3$, δ) : 0.93 (6H, d, J=6.5Hz), 1.02-1.21 (2H, m), 1.45 (9H, s), 1.49-1.72 (9H, m), 1.91-2.12 (2H, m), 2.27 (1H, d, J=2.2Hz), 2.32-2.40 (3H, m), 2.60-2.77 (4H, m), 3.20-3.65 (3H, m), 4.04-4.11 (4H, m), 4.15 (2H, t, J=6.7Hz), 5.03-5.16 (1H, m), 6.71, 7.01 (total 1H, d, J=8.4Hz)

MASS (m/z) : 534 (M^++1)

Example 16

N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-propionyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine phenethyl ester

IR (Film) : 2920, 2850, 1725, 1660, 1630 cm^{-1}

NMR ($CDCl_3$, δ) : 1.01-1.20 (2H, m), 1.36-2.00 (14H, m), 1.57 (9H, s), 2.25 (1H, d, J=2.2Hz), 2.31-2.41 (2H, m), 2.59-2.75 (5H, m), 2.97 (2H, t, J=6.8Hz), 4.02-4.14 (2H, m), 4.29-4.40 (2H, m), 7.17-7.32 (6H, m)

MASS (m/z) : 468 (M^+-Boc+1)

Example 17

N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-

propionyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine phenyl ester

IR (Film) : 3000, 2930, 2855, 1750, 1660, 1620 cm^{-1}

NMR ($CDCl_3$, δ) : 0.97-1.19 (2H, m), 1.45 (9H, s), 1.31-2.13 (11H, m), 2.29-2.40 (3H, m), 2.36 (1H, d, J=2.0Hz), 2.68-2.73 (2H, m), 2.92-3.02 (2H, m), 3.24-3.72 (2H, m), 3.82-3.91 (1H, m), 4.02-4.12 (2H, m), 5.20-5.31 (1H, m), 7.12 (2H, d, J=8.1Hz), 7.18-7.26 (1H, m), 7.35-7.42 (2H, m)

MASS (m/z) : 540 (M^++1)

Example 18

N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-propionyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine 5-indanyl ester

IR (Film) : 2930, 2850, 1750, 1660, 1640 cm^{-1}

NMR ($CDCl_3$, δ) : 0.97-1.18 (2H, m), 1.45 (9H, s), 1.45-1.94 (11H, m), 2.09 (2H, d, J=7.4Hz), 2.30-2.37 (3H, m), 2.36 (1H, d, J=2.3Hz), 2.59-2.72 (2H, m), 2.84-2.94 (6H, m), 3.23-3.69 (2H, m), 3.86-3.95 (1H, m), 4.01-4.11 (2H, m), 5.19-5.31 (1H, m), 6.82-6.87 (1H, m), 6.95 (1H, s), 7.19 (1H, d, J=8.0Hz)

MASS (m/z) : 580 (M^++1)

Example 19

To a solution of N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(R)-methyl-β-alanine (0.97 g) in ethyl acetate (10 ml) was added 4N HCl in ethyl acetate (5.37 ml) at room temperature, and the reaction mixture was stirred for 2 hours. The resulting precipitates were collected by filtration to give N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(R)-methyl-

β-alanine hydrochloride (0.83 g).

IR (KBr pellet) : 2945, 2870, 1726, 1657 cm^{-1}

NMR (DMSO-d_6, δ) : 1.06 (3H, d, J=6.5Hz), 1.21-1.39 (1H, m), 1.47-1.91 (7H, m), 2.10-2.48 (4H, m), 2.58-3.14 (4H, m), 3.20-3.29 (2H, m), 3.87-4.12 (2H, m), 4.15-4.42 (1H, m), 6.45 (1H, d, J=15.2Hz), 6.58 (1H, dd, J=5.4 and 15.2Hz), 7.86-7.95 (1H, m), 8.84-8.98 (1H, br), 9.10-9.21 (1H, br)

MASS (m/z) : 352 (M^+ free+1)

Example 20

To a solution of N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine (1.23 g) in ethyl acetate (12 ml) was added 4N HCl in ethyl acetate (6.66 ml) at room temperature, and the reaction mixture was stirred for 2 hours. The precipitates were filtered, washed with diethyl ether and purified by preparative HPLC eluting with 0.1% trifluoroacetic acid - CH_3CN (9:1), then the fractions containing the object compound were concentrated in vacuo. The residue was resolved in water, neutralized with 1N aq. NaOH, desalted by using the resin of HP-20 eluting with isopropanol - H_2O (1:1), freeze-dried to give N-[(R)-1-[3-(4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine as a white powder (0.7 g).

IR (Film) : 3200, 1660, 1580 cm^{-1}

NMR (DMSO-d_6, δ) : 1.19-1.41 (2H, m), 1.59-1.88 (5H, m), 2.14-2.32 (4H, m), 2.51-2.76 (4H, m), 2.89-3.17 (4H, m), 3.89-4.42 (2H, m), 4.60-4.71 (1H, m), 6.36 (1H, d, J=15.1Hz), 6.57 (1H, dd, J=6.4 and 15.1Hz), 8.85 (1H, br)

MASS (m/z) : 362 (M^++1)

Elemental Analysis Calcd. for $C_{19}H_{27}N_3O_4 \cdot 1.1H_2O$:

C 59.86, H 7.72, N 11.02

Found : C 59.70, H 7.63, N 10.91

The following compounds [Examples 21 and 22] were obtained according to a similar manner to that of Example 20.

Example 21

N-[(R)-1-[3-(4-Piperidyl)propionyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine isohexyl ester

IR (KBr pellet) : 2953, 2936, 2868, 1736, 1657, 1650, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (6H, d, J=6.6Hz), 0.97-1.64 (18H, m), 2.24-2.69 (6H, m), 2.88-3.12 (2H, m), 3.20-3.28 (1H, m), 3.78-3.83 (2H, m), 4.01 (2H, t, J=6.6Hz), 4.11-4.35 (1H, m), 4.80-4.92 (1H, m), 8.40-8.49 (1H, m)

MASS (m/z) : 448 (M^++1)

Elemental Analysis Calcd. for $C_{25}H_{41}N_3O_4 \cdot H_2O$:

C 64.49, H 9.31, N 9.02

Found : C 64.52, H 9.32, N 9.04

Example 22

N-[(R)-1-[3-(4-Piperidyl)propionyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine isopentyl ester

IR (KBr pellet) : 3037, 2953, 2934, 2868, 1736, 1641, 1626 cm^{-1}

NMR (DMSO-d_6, δ) : 0.88 (6H, d, J=6.5Hz), 0.97-1.77 (15H, m), 2.14-2.68 (6H, m), 2.87-3.12 (3H, m), 3.20-3.24 (1H, m), 3.68-3.84 (2H, m), 4.06 (2H, t, J=6.7Hz), 4.13-4.34 (2H, m), 4.78-4.92 (1H, m), 8.40-8.51 (1H, m)

MASS (m/z) : 434 (M^++1)

Example 23

To a solution of N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)propionyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine phenethyl ester (0.53 g) in ethyl acetate (5 ml) was added 4N HCl in ethyl acetate (2.33 ml) at room temperature, and the reaction mixture was stirred for 2 hours. The resulting precipitates were collected by filtration to give N-[(R)-1-[3-(4-piperidyl)propionyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine phenethyl ester hydrochloride (0.46 g).

IR (KBr pellet) : 3028, 2945, 2864, 2804, 1736, 1651 cm^{-1}

NMR (DMSO-d_6, δ) : 1.21-1.75 (11H, m), 2.30-2.35 (2H, m), 2.61-3.10 (8H, m), 2.88 (3H, t, J=6.8Hz), 3.17-3.29 (2H, m), 3.66-3.84 (1H, m), 4.24 (2H, d, J=7.0Hz), 4.69-4.92 (1H, m), 7.20-7.35 (5H, m), 8.45-8.55 (1H, m), 8.46-8.65 (1H, br), 8.81-8.93 (1H, br)

MASS (m/z) : 468 (M^+ free+1)

The following compounds [Examples 24 to 29] were obtained according to a similar manner to that of Example 23.

Example 24

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3-phenyl-β-alanine hydrochloride

IR (Nujol) : 1725, 1645 cm^{-1}

NMR (DMSO-d_6, δ) : 1.16-1.91 (7H, m), 2.20-2.50 (4H, m), 2.60-3.00 (5H, m), 3.19-3.31 (3H, m), 4.15-4.46 (1H, m), 5.18 (1H, q, J=7.7Hz), 6.44 (1H, d, J=15.3Hz), 6.59 (1H, dd, J=15.3 and 5.2Hz), 7.19-7.32 (5H, m), 8.47-8.60 (1H, m), 8.91-9.05 (1H, br), 9.18-9.30 (1H, br)

MASS (m/z) : 414 (M^+ free+1)

Example 25

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(R)-phenethyl-β-alanine hydrochloride

IR (KBr pellet) : 3061, 3026, 2949, 2860, 1724, 1653 cm^{-1}

NMR (DMSO-d_6, δ) : 1.26-1.42 (1H, m), 1.49-1.85 (9H, m), 2.15-3.05 (10H, m), 3.18-3.31 (2H, m), 3.89-4.08 (2H, m), 4.20-4.42 (1H, m), 6.46 (1H, d, J=15.2Hz), 6.59 (1H, dd, J=5.3 and 15.2Hz), 7.16-7.30 (5H, m), 7.89-8.00 (1H, m), 8.88-9.00 (1H, br), 9.15-9.26 (1H, br)

MASS (m/z) : 442 (M^+ free+1)

[α] = -28.8° (C=1.0, MeOH)

Elemental Analysis Calcd. for $C_{25}H_{35}N_3O_4HCl \cdot 3.5H_2O$: C 56.50, H 8.01, N 7.77

Found : C 56.56, H 7.77, N 7.57

Example 26

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2(S)-acetylamino-β-alanine hydrochloride

IR (KBr pellet) : 3076, 2953, 2864, 1728, 1657 cm^{-1}

NMR (DMSO-d_6, δ) : 1.21-1.99 (10H, m), 1.85 (3H, s), 2.11-2.51 (2H, m), 2.57-3.11 (2H, m), 3.18-3.32 (2H, m), 3.35-3.48 (1H, m), 3.90-4.07 (1H, m), 4.17-4.45 (3H, m), 6.40-6.65 (2H, m), 8.07-8.27 (2H, m), 8.73-8.89 (1H, br), 9.00-9.13 (1H, br)

MASS (m/z) : 395 (M^+ free+1)

[α] = -29.2° (C=1.0, MeOH)

Example 27

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2(S)-benzoylamino-β-alanine hydrochloride

IR (KBr pellet) : 2970, 2868, 1728, 1655, 1603 cm^{-1}

NMR (DMSO-d_6, δ) : 1.14-1.99 (9H, m), 2.14-2.50 (2H, m), 2.57-3.11 (3H, m), 3.17-3.26 (2H, m), 3.37-3.50 (2H, m), 3.86-4.57 (3H, m), 6.43 (1H, d, J=15.4Hz), 6.57 (1H, dd, J=15.4 and 5.5Hz), 7.45-7.56 (3H, m), 7.89 (2H, d, J=6.6Hz), 8.21-8.37 (1H, m), 8.62-8.86 (2H, m), 9.00-9.12 (1H, br)

MASS (m/z) : 457 (M^+ free+1)

[α] = -45.3° (C=1.0, MeOH)

Example 28

N-[(R)-1-[3-(4-Piperidyl)propionyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine phenyl ester

IR (KBr pellet) : 3043, 2953, 2862, 1755, 1653, 1616 cm^{-1}

NMR (DMSO-d_6, δ) : 1.21-1.91 (12H, m), 2.06-2.38 (2H, m), 2.55-3.11 (7H, m), 3.13-3.28 (2H, m), 3.35-3.39 (1H, m), 3.67-3.85 (1H, m), 4.95-5.08 (1H, m), 7.11-7.44 (5H, m), 8.69 (1H, dd, J=16.1 and 8.3Hz), 8.59-8.73 (1H, br), 8.88-9.00 (1H, br)

MASS (m/z) : 440 (M^+ free+1)

Example 29

N-[(R)-1-[3-(4-Piperidyl)propionyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine 5-indanyl ester

IR (KBr pellet) : 2945, 2862, 2812, 1755, 1653, 1616 cm^{-1}

NMR (DMSO-d_6, δ) : 1.22-1.86 (9H, m), 1.98-2.22 (2H, m), 2.27-2.40 (2H, m), 2.59-2.85 (11H, m), 3.15-3.26 (2H, m), 3.35-3.40 (1H, m), 3.69-3.85 (1H, m), 4.10-4.37 (1H, m), 4.92-5.04 (1H, m), 6.80-6.85 (2H, m), 6.94 (1H, s) 7.23 (2H, d, J=7.9Hz), 8.40-8.52 (1H, m), 8.60-8.68 (1H, m),

8.63-8.80 (1H, br)

MASS (m/z) : 480 (M^+ free+1)

Example 30

To the solution of N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)propionyl]-3-piperidylcarbonyl]-3(S)-(3-methyl-5-isoxazolyl)-β-alanine ethyl ester (0.8 g) in MeOH (10 ml) was added 1N aqueous NaOH (2.3 ml) at 0°C. The reaction mixture was stirred at room temperature for 2 hours, and then the solvent was removed in vacuo. The residue was dissolved in ethyl acetate - water, and acidified with 10% aqueous $KHSO_4$. The organic layer was separated and evaporated in vacuo. The residue was dissolved in ethyl acetate (8 ml), and then a solution of 4N HCl in ethyl acetate (4 ml) was added. The whole was stirred at room temperature for 2 hours, and then the solvent was removed in vacuo. The residue was powdered from diethyl ether to give N-[(R)-1-[3-(4-piperidyl)propionyl]-3-piperidylcarbonyl]-3(S)-(3-methyl-5-isoxazolyl)-β-alanine hydrochloride (0.46 g) as a white solid.

IR (KBr pellet) : 3446, 2931, 1734, 1652, 1608 cm^{-1}

NMR (D_2O, δ) : 1.35-1.78 (8H, m), 1.93-2.00 (3H, s), 2.26 (3H, s), 2.45-2.53 (3H, m), 2.80-3.25 (6H, m), 3.39-3.45 (2H, m), 3.77-3.83 (1H, m), 4.08-4.22 (1H, m), 5.44-5.51 (1H, m), 6.24 (1H, d, J=2.2Hz)

MASS (m/z) : 421 (M^+ free+1)

Example 31

To a mixture of (R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidinecarboxylic acid (2 g) and β-alanine ethyl ester hydrochloride (0.84 g) and 1-hydroxybenzotriazole (0.74 g) in dimethylformamide (20 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1

ml) at 0°C. The reaction mixture was stirred overnight at room temperature, and then poured into water. The whole was extracted with ethyl acetate, washed with aqueous saturated $NaHCO_3$, water, and brine, dried over $MgSO_4$, and evaporated in vacuo, subsequently. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$-MeOH (99:1) to give N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-β-alanine ethyl ester as a colorless oil (2.54 g).

IR (Film) : 2960, 2930, 2850, 1725, 1650, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.27 (3H, t, J=7.1Hz), 1.31-1.40 (2H, m), 1.46 (9H, S), 1.63-1.78 (2H, m), 1.69-1.97 (6H, m), 2.20-2.37 (2H, m), 2.52 (2H, t, J=6.1Hz), 2.69-2.83 (2H, m), 3.28 (1H, dd, J=13.5 and 9.5Hz), 3.47-3.56 (2H, m), 4.07-4.17 (3H, m), 4.16 (2H, q, J=7.1Hz), 6.23 (1H, d, J=15.1Hz), 6.45-6.64 (1H, m), 6.81 (1H, dd, J=15.1 and 6.7Hz)

MASS (m/z) : 466 (M^++1)

Example 32

A solution of LiOH (0.18 g) in water (10 ml) was added to a solution of N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-β-alanine ethyl ester (1.74 g) in the mixture of tetrahydrofuran (10 ml) and ethanol (10 ml) at 0°C. The reaction mixture was stirred for overnight at room temperature, and the solvent was evaporated in vacuo. The residue was resolved in ethyl acetate-water, and acidified with 10% aqueous $KHSO_4$. The whole was washed with water, brine, dried over $MgSO_4$, and evaporated in vacuo to give N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-β-alanine as a colorless oil (1.64 g).

IR (Film) : 2930, 2855, 1720, 1625 cm^{-1}

NMR (DMSO-d_6, δ) : 1.14-1.31 (2H, m), 1.39 (9H, s), 1.50-1.85 (6H, m), 2.11-2.31 (2H, m), 2.37 (2H, t, J=6.8Hz), 2.56-3.29 (7H, m), 3.90-4.01 (2H, m), 4.17-4.43 (1H, m), 6.43 (1H, d, J=15.2Hz), 6.60 (1H, dd, J=15.2 and 6.3Hz), 7.99 (1H, t, J=5.4Hz), 12.13 (1H, br)

MASS (m/z) : 438 (M^++1)

Example 33

To a solution of N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-β-alanine ethyl ester (0.8 g) in ethyl acetate (8 ml) was added 4N HCl in ethyl acetate (4.3 ml) at 0°C, and the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was concentrated in vacuo, and resolved in water, neutralized with saturated aqueous $NaHCO_3$, desalted by using the resin of HP-20 eluting with isopropanol-H_2O (1:1), then freeze-dried to give N-[(R)-1-[3-(4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-β-alanine ethyl ester (458 mg).

IR (KBr pellet) : 3406, 2993, 2945, 2856, 2821, 2735, 1730, 1655 cm^{-1}

NMR (D_2O, δ) : 1.27 (3H, t, J=7.1Hz), 1.46-1.88 (6H, m), 1.92-2.07 (3H, m), 2.39-2.57 (2H, m), 2.60 (2H, t, J=6.2Hz), 2.96-3.30 (4H, m), 3.39-3.49 (4H, m), 3.95-4.38 (2H, m), 4.17 (2H, q, J=7.1Hz), 6.48 (1H, d, J=15.7Hz), 6.60-6.73 (1H, m)

MASS (m/z) : 366 (M^++1)

Example 34

To a solution of N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-β-alanine (1.64 g) in ethyl acetate (16 ml) was added 4N HCl

in ethyl acetate (9.37 ml) at 0°C, and the reaction mixture was stirred for 2 hours at room temperature. The precipitates were filtered, washed with ether and resolved in water, neutralized with saturated aqueous $NaHCO_3$, desalted by using the resin of HP-20 eluting with isopropanol-H_2O (1:1), then freeze-dried to give N-[(R)-1-[3-(4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-β-alanine as a white powder (690 mg).

IR (KBr pellet) : 3392, 3074, 2943, 2862, 2746, 2522, 1652 cm^{-1}

NMR (D_2O, δ) : 1.42-2.09 (9H, m), 2.39 (2H, t, J=6.8Hz), 2.43-2.70 (2H, m), 2.94-3.16 (3H, m), 3.20-3.51 (5H, m) 3.97-4.38 (2H, m), 6.47 (1H, d, J=15.5Hz), 6.59-6.72 (1H, m)

MASS (m/z) : 339 (M^++1)

$[\alpha]_D^{20}$ = -43.17° (C=1.0, MeOH)

Example 35

To a mixture of 3(R)-(3,4-dimethoxyphenethyl)-β-alanine methyl ester (0.87 g), (R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidinecarboxylic acid (1.19 g) and 1-hydroxybenztriazole (0.44 g) in dimethylformamide (9 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.59 ml) at 0°C. The reaction mixture was stirred overnight at room temperature, and then poured into water. The whole was extracted with ethyl acetate, washed with aqueous saturated $NaHCO_3$, water, and brine, dried over $MgSO_4$, and evaporated in vacuo, subsequently. The residue was purified by column chromatography on silica gel eluting with ethyl acetate: n-hexane = (5:1) to give N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(R)-(3,4-dimethoxyphenethyl)-β-alanine methyl ester as a colorless oil (1.83 g).

IR (Film) : 2980, 2930, 2850, 1730, 1650, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.26-1.40 (2H, m), 1.46 (9H, s), 1.68-1.91 (7H, m), 2.22-2.40 (3H, m), 2.49-2.82 (6H, m), 3.35-3.69 (2H, m), 3.65 (3H, s), 3.85 (3H, s), 3.87 (3H, s), 3.94-4.17 (3H, m), 4.26-4.37 (1H, m), 6.18-6.36 (2H, m), 6.72-6.86 (5H, m)

MASS (m/z) : 616 (M^++1)

The following compounds [Examples 36 to 64] were obtained according to a similar manner to that of Example 35.

Example 36

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester

IR (Film) : 3260, 1730, 1690, 1640, 1620 cm^{-1}

NMR ($CDCl_3$, δ) : 1.24-1.31 (3H, m), 1.47 (9H, s), 1.50-1.55 (2H, br), 1.88-2.04 (2H, m), 2.27 (1H, d, J=2.4Hz), 2.35 (3H, br), 2.68-2.71 (2H, m), 3.40 (2H, br), 3.54-3.60 (2H, m), 3.65-3.75 (1H, m), 4.07-4.18 (6H, m), 5.09 (1H, br), 6.03 (1H, br), 7.28 (1H, d, J=15.0Hz)

Example 37

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(Z)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester

IR (Film) : 3250, 1720, 1690, 1640, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.26 (3H, t, J=7.2Hz), 1.20-1.46 (2H, m), 1.46 (9H, s), 1.65-1.77 (4H, m), 1.90-2.13 (3H, m), 2.29 (1H, d, J=2.4Hz), 2.35 (1H, br), 2.73-2.91 (5H, m), 3.18-3.30 (2H, m), 3.67-3.94 (1H, m), 3.94-4.24 (2H, m), 4.18 (2H, t, J=7.2Hz), 5.09-5.11 (1H, m), 5.67-5.77 (1H, m), 5.93-6.04 (1H, m)

MASS (m/z) : 490 (M^++1)

Example 38

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-(3-methyl-5-isoxazolyl)-β-alanine ethyl ester

IR (Film) : 3420, 3250, 1730, 1670, 1660, 1590 cm^{-1}

NMR ($CDCl_3$, δ) : 1.20-1.29 (6H, m), 1.46 (9H, s), 1.71-1.77 (4H, m), 1.90 (1H, br), 2.26 (3H, s), 2.30-2.45 (2H, m), 2.70-2.90 (4H, m), 3.39-3.65 (2H, m), 4.06-4.17 (6H, m), 5.54-5.58 (1H, m), 6.00 (1H, s), 6.23 (1H, d, J=15.5Hz), 6.82 (1H, dd, J=6.6 and 15.5Hz)

Example 39

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl-3(R)-(4-methoxyphenethyl)-β-alanine methyl ester

IR (Film) : 2930, 2840, 1725, 1680, 1660, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-1.40 (2H, m), 1.46 (9H, s), 1.44-1.95 (8H, m), 2.19-2.39 (3H, m), 2.48-2.84 (6H, m), 3.32-3.70 (5H, m), 3.78 (3H, s), 3.97-4.35 (4H, m), 6.16-6.35, 6.74-6.86 (total 2H, m), 6.78 (3H, q, J=6.9Hz), 7.09 (2H, d, J=8.5Hz)

MASS (m/z) : 586 (M^++1)

Example 40

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-methoxymethyl-β-alanine methyl ester

IR (Film) : 2955, 2850, 1720, 1640, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.15-1.77 (9H, m), 1.46 (9H, s), 1.89-2.07 (2H, m), 2.23-2.38 (2H, m), 2.59 (2H, d, J=6.1Hz), 2.70-2.81 (3H, m), 3.20-3.51 (2H, m), 3.34 (3H, s), 3.96-4.29 (3H, m), 4.36-4.50 (1H, m), 3.68 (3H, m), 6.23 (1H, d, J=15.3Hz), 6.82 (1H, dd, J=15.3 and 6.7Hz)

MASS (m/z) : 496 (M^++1)

Example 41

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3-ethynyl-β-alanine ethyl ester

IR (Film) : 3250, 2960, 2920, 2850, 1710, 1650, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.14-1.61 (6H, m), 1.46 (9H, s), 1.69-1.80 (3H, m), 1.90-2.05 (2H, m), 2.23-2.40 (2H, m), 2.28 (1H, d, J=2.4Hz), 2.61-2.81 (4H, m), 3.27-3.38 (2H, m), 3.65-3.80 (1H, m), 4.07-4.24 (5H, m), 5.04-5.17 (1H, m), 6.24 (1H, d,

J=15.0Hz), 6.82 (1H, dd, J=15.0 and 6.7Hz), 7.03-7.23 (1H, m)

MASS (m/z) : 490 (M^++1)

Example 42

N-[(S)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3-ethynyl-β-alanine ethyl ester

IR (Film) : 2960, 2925, 2850, 1715, 1650, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.28 (3H, t, J=7.1Hz), 1.22-1.60 (4H, m), 1.46 (9H, s), 1.69-1.77 (4H, m), 1.89-2.05 (1H, m), 2.23-2.40 (2H, m), 2.28 (1H, d, J=2.4Hz), 2.69-2.82 (4H, m), 3.25-3.43 (2H, m), 3.65-3.78 (1H, m), 4.10-4.20 (4H, m), 5.04-5.15 (1H, m), 6.30 (1H, d, J=15.2Hz), 6.82 (1H, dd, J=15.2 and 6.6Hz), 6.61-6.77, 7.05-7.15 (total 1H, m)

MASS (m/z) : 490 (M^++1)

Example 43

N-[1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-4-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester

IR (Film) : 3030, 2970, 2825, 2850, 1730, 1645, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.29 (3H, t, J=7.1Hz), 1.25-1.50 (2H, m), 1.46 (9H, s), 1.57-1.79 (3H, m), 1.84-1.96 (2H, m), 2.20-2.44 (2H, m), 2.28 (1H, d, J=2.4Hz), 2.68-2.82 (6H, m), 2.99-3.15 (1H, m), 3.95-4.24 (5H, m), 4.54-4.68 (1H, m), 5.06-5.16 (1H, m), 6.22 (1H, d, J=15.2Hz), 6.60 (1H, d, J=8.7Hz), 6.80 (1H, dd, J=15.2 and 6.7Hz)

MASS (m/z) : 490 (M^++1)

Example 44

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-trifluoroacetylaminomethyl-β-alanine tert-butyl ester

Example 45

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2(S)-(4-trifluoromethylbenzoylamino)-β-alanine ethyl ester

IR (Nujol) : 1730 cm^{-1}

NMR ($CDCl_3$, δ) : 1.05-1.40 (2H, m), 1.29 (3H, t, J=7.3Hz), 1.45 (9H, s), 1.45-1.75 (4H, m), 2.05-2.45 (2H, m), 2.45-2.85 (3H, m), 3.20-3.60 (3H, m), 3.60-3.95 (2H, m), 3.95-4.30 (6H, m), 4.75-4.95 (1H, m), 6.18 (1H, d, J=15.3Hz), 6.64 (1H, dd, J=15.3 and 6.4Hz), 7.72 (3H, d-like), 7.85-8.25 (3H, m)

MASS (m/z) : 653 (M^++1)

Example 46

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2(S)-trifluoroacetylamino-β-alanine ethyl ester

NMR ($CDCl_3$, δ) : 1.20-1.40 (2H, m), 1.26 (3H, t, J=7.2Hz), 1.50-1.95 (6H, m), 2.10-2.45 (2H, m), 2.45-2.90 (3H, m), 3.20-3.55 (2H, m), 3.55-3.90 (1H, m), 3.95-4.45 (7H, m), 4.60-4.80 (1H, m), 6.21 (1H, d, J=15.3Hz), 6.81 (1H, dd, J=15.2 and 6.6Hz), 8.30-8.55 (1H, br)

MASS (m/z) : 577 (M^++1)

Example 47

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-3-azetidinyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester

IR (Neat) : 1660 cm^{-1}

NMR ($CDCl_3$, δ) : 1.29 (3H, t, J=7.1Hz), 1.35-1.60 (1H, m), 1.44 (9H, s), 1.60-2.15 (2H, m), 2.15-2.45 (2H, m), 2.50-2.85 (3H, m), 3.10-3.50 (3H, m), 3.55-4.05 (5H, m), 4.05-4.30 (5H, m), 5.00-5.20 (1H, m), 6.20-6.40 (1H, m), 6.60-6.85 (1H, br), 7.00 (1H, dd, J=15.0 and 8.2Hz)

MASS (m/z) : 462 (M^++1)

Example 48

N-[(R)-1-[4-(1-tert-Butoxycarbonyl-3-azetidinyl)-(E)-2-butenoyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester

NMR ($CDCl_3$, δ) : 1.28 (3H, t, J=7.1Hz), 1.35-2.00 (7H, m), 1.43 (9H, s), 2.20-2.85 (6H, m), 2.28 (1H, d, J=2.4Hz), 3.05-3.85 (4H, m), 4.02 (2H, t, J=8.5Hz), 4.10-4.23 (2H, m), 5.05-5.15 (1H, m), 6.15-6.40 (1H, m), 6.68-6.83 (1H, m), 6.85-7.15 (1H, m)

MASS (m/z) : 476 (M^++1)

Example 49

N-[(R)-1-[(2-tert-Butoxycarbonyl-1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester

IR (Nujol) : 1670 cm^{-1}

NMR ($CDCl_3$, δ) : 1.28 (3H, t, J=7.1Hz), 1.35-2.15 (6H, m), 1.49 (9H, s), 2.29 (1H, d, J=2.3Hz), 2.35-3.00 (5H, m), 3.00-3.60 (2H, m), 3.65 (2H, t, J=5.8Hz), 4.05-4.40 (1H, m), 4.18 (2H, q, J=7.1Hz), 4.58 (2H, s), 5.00-5.25 (1H, m), 7.05-7.25 (3H, m)

MASS (m/z) : 512 (M^++1)

Example 50

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-

methacryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester

IR (Neat) : 1730, 1660 cm^{-1}

NMR ($CDCl_3$, δ) : 1.15-1.55 (2H, m), 1.29 (3H, t, J=7.1Hz), 1.46 (9H, s), 1.55-1.80 (5H, m), 1.80-2.05 (2H, m), 1.87 (3H, d, J=1.4Hz), 2.20-2.55 (2H, m), 2.28 (3H, d, J=2.4Hz), 2.55-2.90 (4H, m), 3.00-3.50 (1H, m), 3.50-3.95 (1H, m), 4.00-4.20 (2H, m), 4.19 (2H, q, J=7.1Hz), 5.00-5.20 (1H, m), 5.33 (1H, d, J=9.1Hz)

Example 51

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3,3-dimethyl-β-alanine ethyl ester

NMR ($CDCl_3$, δ) : 1.26 (3H, t, J=7.1Hz), 1.25-1.40 (2H, m), 1.41 (3H, s), 1.33 (3H, s), 1.41 (9H, s), 1.50-1.75 (5H, m), 1.80-2.05 (2H, m), 2.10-2.40 (2H, m), 2.60-2.85 (4H, m), 3.10-3.35 (2H, m), 3.60-3.90 (1H, m), 4.00-4.35 (2H, m), 4.13 (2H, q, J=7.1Hz), 6.05-6.45 (2H, m), 6.81 (1H, dd, J=15.3 and 6.7Hz)

MASS (m/z) : 494 (M^++1)

Example 52

N-[(R)-1-[2-[1-tert-Butoxycarbonyl-4-piperidyl]-(1R*,2S*)-cyclopropan-1-yl]carbonyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester

IR (Neat) : 1730, 1660 cm^{-1}

NMR ($CDCl_3$, δ) : 0.60-1.05 (3H, m), 1.05-1.40 (9H, m), 1.45 (9H, s), 1.50-1.85 (8H, m), 1.85-2.20 (2H, m), 2.20-2.50 (2H, m), 2.50-2.90 (4H, m), 3.15-3.55 (2H, m), 3.60-4.30 (6H, m), 5.00-5.20 (1H, m)

MASS (m/z) : 504 (M^++1)

Example 53

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-3-methyl-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester

IR (Neat) : 1740, 1670, 1610 cm^{-1}

NMR ($CDCl_3$, δ) : 1.29 (3H, t, J=7.1Hz), 1.30-1.55 (2H, m), 1.46 (9H, s), 1.55-1.80 (2H, m), 1.84 (3H, s), 1.85-2.25 (2H, m), 2.25-2.45 (1H, m), 2.26 (1H, d, J=2.4Hz), 2.55-2.85 (5H, m), 3.05-3.40 (2H, m), 3.50-3.80 (1H, m), 4.05-4.35 (4H, m), 5.00-5.20 (1H, m), 5.70-5.90 (1H, m)

Example 54

N-[(R)-1-[4-(1-tert-Butoxycarbonyl-3-piperidyl)-(E)-2-butenoyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester

IR (Neat) : 1730, 1680, 1660 cm^{-1}

NMR ($CDCl_3$, δ) : 1.00-2.40 (12H, m), 1.28 (3H, m), 1.45 (9H, s), 2.40-2.90 (5H, m), 3.05-3.45 (3H, m), 3.50-4.30 (4H, m), 4.18 (2H, q, J=7.1Hz), 5.00-5.20 (1H, m), 6.27 (1H, d, J=15.0Hz), 6.65-7.00 (1H, m)

MASS (m/z) : 504 (M^++1)

Example 55

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-β-alanine 1-(cyclohexyloxycarbonyloxy)ethyl ester

IR (Film) : 2930, 2850, 1750, 1650, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.26-1.58 (15H, m), 1.51 (9H, s), 1.69-1.81 (6H, m), 1.89-2.00 (4H, m), 2.20-2.38 (2H, m), 2.55 (2H, t, J=6.0Hz), 2.70-2.84 (2H, m), 3.20-3.34 (1H, m), 3.44-3.61 (2H, m), 4.07-4.17 (2H, m), 4.57-4.91 (1H, m), 6.25 (1H, d, J=15.3Hz), 6.69-6.79 (1H, m), 6.81 (1H, dd, J=15.3 and 6.7Hz)

MASS (m/z) : 608 (M^++1)

Example 56

Methyl 3-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]aminobenzoate

IR (Film) : 3070, 3000, 2940, 2850, 1710, 1680, 1650, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.29-1.47 (2H, m), 1.45 (9H, s), 1.57-2.00 (5H, m), 2.21-2.40 (2H, m), 2.59-2.84 (3H, m), 3.54-3.61 (2H, m), 3.90 (3H, s), 3.90-3.96 (2H, m), 4.05-4.17 (2H, m), 6.24 (1H, d, J=15.3Hz), 6.90 (1H, dd, J=15.1 and 6.4Hz), 7.38 (1H, t, J=8.0Hz), 7.75-7.86 (2H, m), 8.27 (1H, s), 9.25 (1H, s)

MASS (m/z) : 500 (M^++1)

Example 57

Ethyl 4-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]aminobenzoate

IR (Film) : 3100, 2980, 2930, 2850, 1700, 1660, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.26-1.46 (2H, m), 1.39 (3H, t, J=7.1Hz), 1.46 (9H, s), 1.57-1.79 (5H, m), 2.21-2.45 (2H, m), 2.66-2.84 (3H, m), 3.48-3.80 (3H, m), 4.06-4.23 (3H, m), 4.36 (2H, q, J=7.1Hz), 6.23 (1H, d, J=14.4Hz), 6.84-6.95 (1H, m), 7.73 (2H, d, J=8.6Hz), 8.00 (2H, d, J=8.6Hz), 9.36 (1H, s)

MASS (m/z) : 514 (M^++1)

Example 58

Methyl 2-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]aminobenzoate

IR (Film) : 2960, 2925, 2850, 1720, 1650, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.26-1.46 (2H, m), 1.46 (9H, s), 1.70-1.91 (6H, m), 2.13-2.37 (2H, m), 2.45-2.60 (1H, m), 2.68-2.84 (2H, m), 2.90-3.46 (2H, m), 3.94 (3H, s), 4.04-4.19 (3H, m), 6.34 (1H, d, J=15.2Hz), 6.84 (1H, dd, J=15.2 and 2.6Hz), 7.05-7.14 (total 1H, m), 7.51-7.60 (1H, m), 8.03-8.07 (1H, m), 8.69 (1H, d, J=8.5Hz), 11.19-11.34 (1H, m)

MASS (m/z) : 500 (M^++1)

Example 59

Methyl 3-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)propanoyl]-3-piperidylcarbonyl]aminobenzoate

IR (Film) : 2930, 1715, 1660, 1610 cm^{-1}

NMR ($CDCl_3$, δ) : 0.97-1.19 (2H, m), 1.45 (9H, s), 1.52-1.95 (9H, m), 2.27-2.45 (3H, m), 2.53-2.74 (3H, m), 3.38-3.59 (1H, m), 3.70-3.80 (1H, m), 3.91 (3H, s), 4.00-4.12 (3H, m), 7.38 (1H, t, J=7.9Hz), 7.75-7.84 (2H, m), 8.26 (1H, s), 8.89 (1H, s)

MASS (m/z) : 402 (M^+-Boc+1)

Example 60

Ethyl 4-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)propanoyl]-3-piperidylcarbonyl]aminobenzoate

IR (Film) : 2960, 2930, 2850, 1680, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 0.98-1.18 (2H, m), 1.38 (3H, t, J=7.1Hz), 1.44 (9H, s), 1.51-1.97 (8H, m), 2.25-2.45 (3H, m), 2.53-2.69 (3H, m), 3.46-3.54 (2H, m), 3.76-3.84 (1H, m), 3.93-4.10 (3H, m), 4.35 (2H, q, J=7.1Hz), 7.70 (2H, d, J=8.7Hz), 7.99 (2H, d, J=8.7Hz), 9.20 (1H, s)

MASS (m/z) : 416(M^+-Boc+1)

Example 61

Methyl 2-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)propanoyl]-3-piperidylcarbonyl]aminobenzoate

IR (Film) : 3260, 2960, 2920, 2850, 1715, 1670, 1620, 1610 cm^{-1}

NMR ($CDCl_3$, δ) : 1.02-1.22 (2H, m), 1.45 (9H, s), 1.57-1.93 (7H, m), 2.37-3.40 (9H, m), 3.94 (3H, s), 4.00-4.15 (3H, m), 4.39-4.89 (1H, m), 7.05-7.17 (1H, m), 7.51-7.60 (1H, m), 8.01-8.10 (1H, m), 8.67-8.72 (1H, m), 11.18-11.33 (1H, m)

MASS (m/z) : 502 (M^+-Boc+1)

Example 62

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-propanoyl]-3-piperidylcarbonyl]-3(S)-methoxymethyl-β-alanine methyl ester

IR (Film) : 2910, 2850, 1725, 1670, 1620 cm^{-1}

NMR ($CDCl_3$, δ) : 1.03-1.26 (2H, m), 1.45 (9H, s), 1.37-2.07 (6H, m), 2.20-2.42 (4H, m), 2.54-2.73 (6H, m), 3.19-3.48 (5H, m), 3.34 (3H, s), 3.67 (3H, s), 4.03-4.16 (3H, m), 4.33-4.49 (1H, m), 6.31-6.67 (1H, m)

MASS (m/z) : 498 (M^++1)

Example 63

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridyl)propanoyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester

IR (Film) : 3260, 1730, 1600 (br) cm^{-1}

NMR ($CDCl_3$, δ) : 1.25-1.32 (4H, m), 1.46 (9H, s), 1.70-1.75 (4H, br), 1.99-2.05 (4H, m), 2.27 (1H, d, J=2.4Hz), 2.35-2.41 (4H, br), 2.67-2.71 (2H, m), 3.28-3.31 (2H, m), 3.46-3.52 (2H, m), 3.85 (2H, br), 4.07-4.19 (2H, m), 5.09 (1H, br), 5.38 (1H, br)

Example 64

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridyl)propanoyl]-3-piperidylcarbonyl]-3(S)-(3-methyl-5-isoxazolyl)-β-alanine ethyl ester

IR (Film) : 3260, 1720, 1650 (br) cm^{-1}

NMR ($CDCl_3$, δ) : 1.21-1.30 (4H, m), 1.46 (9H, s), 1.55-2.07 (6H, m), 2.62 (3H, s), 2.20-2.50 (4H, m), 2.88-2.96 (2H, m), 3.22-3.52 (4H, m), 3.85 (1H, br), 3.98 (1H, br), 4.13 (3H, q, J=7.1Hz), 5.38 (1H, br), 5.51-5.61 (1H, m), 5.99 (1H, br)

MASS (m/z) : 447 (M^++1-Boc)

Example 65

To a solution of N-tert-butoxycarbonyl-2-hydroxymethyl-β-alanine ethyl ester (0.5 g) in ethyl acetate (5 ml) was added 4N HCl in ethyl acetate (5.05 ml) at 0°C, and the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was concentrated in vacuo. The residue, (R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidinecarboxylic acid (0.74 g) and 1-hydroxybenztriazole (0.27 g) was dissolved in dimethylformamide (5 ml), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.55 ml) was added under stirring at 0°C. After stirring at ambient temperature for overnight, the mixture was poured into water. The whole was extracted with ethyl acetate, washed with aqueous saturated $NaHCO_3$, water, and brine, dried over $MgSO_4$, and evaporated in vacuo, subsequently. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$:MeOH = (99:1) to give N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2-hydroxymethyl-β-alanine ethyl ester as a colorless oil (0.37 g, 36.9%).

IR (Film) : 2970, 2930, 2850, 1720, 1645, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.28 (3H, t, J=7.1Hz), 1.32-1.46 (2H, m), 1.46 (9H, s), 1.53-2.14 (8H, m), 2.23-2.48 (2H, m), 2.70-2.81 (3H, m), 3.34-3.85 (5H, m), 3.99-4.19 (3H, m), 4.17 (2H, q, J=7.1Hz), 6.23 (1H, d, J=15.1Hz), 6.82 (1H, dd, J=15.2 and 6.7Hz), 6.88-7.01 (1H, m)

MASS (m/z) : 496 (M^++1)

The following compounds [Examples 66 to 72] were obtained according to a similar manner to that of Example 65.

Example 66

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2-benzyloxymethyl-β-alanine ethyl ester

IR (Film) : 2980, 2940, 2870, 1730, 1680, 1660 cm^{-1}

NMR ($CDCl_3$, δ) : 1.26 (3H, t, J=7.1Hz), 1.25-1.46 (5H, m), 1.46 (9H, s), 1.63-1.91 (4H, m), 2.16-2.35 (2H, m), 2.68-2.88 (3H, m), 3.13-3.24 (1H, m), 3.52-3.80 (5H, m), 4.05-4.19 (3H, m), 4.17 (2H, q, J=7.1Hz), 4.50 (2H, s), 6.23 (1H, d, J=15.2Hz), 6.44-6.53 (1H, m), 6.80 (1H, dd, J=15.2 and 6.7Hz), 7.27-7.35 (5H, m)

MASS (m/z) : 586 (M^++1)

Example 67

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-benzoyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester

IR (Film) : 3000, 2970, 2860, 1725, 1670, 1620 cm^{-1}

NMR ($CDCl_3$, δ) : 1.28 (3H, t, J=7.1Hz), 1.20-1.31 (1H, m), 1.48 (9H, s), 1.40-2.04 (11H, m), 2.28 (1H, d, J=2.3Hz), 2.34-2.89 (6H, m), 4.11-4.31 (5H, m), 5.06-5.16 (1H, m), 7.21-7.54 (4H, m)

MASS (m/z) : 540 (M^++1)

Example 68

N-[(R)-1-[4-(1-tert-Butoxycarbonyl-4-piperidyl)-benzoyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester

IR (Film) : 3400, 2960, 2925, 2850, 1730, 1665, 1615 cm^{-1}

NMR ($CDCl_3$, δ) : 1.26 (3H, t, J=7.1Hz), 1.48 (9H, s), 1.57-2.04 (11H, m), 2.28 (1H, d, J=2.4Hz), 2.36-2.86 (6H, m), 7.12 (2H, q, J=7.1Hz), 4.20-4.28 (3H, m), 5.07-5.17 (1H, m), 7.23 (2H, d, J=8.2Hz), 7.27 (1H, s), 7.35 (2H, d, J=8.2Hz)

MASS (m/z) : 540 (M^++1)

Example 69

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-propanoyl]-3-piperidylcarbonyl]-2-benzyloxymethyl-β-alanine ethyl ester

IR (Film) : 2980, 2930, 2860, 1735, 1660, 1635 cm^{-1}

NMR ($CDCl_3$, δ) : 1.01-1.20 (2H, m), 1.26 (3H, t, J=7.1Hz), 1.35-1.73 (10H, m), 1.45 (9H, s), 1.79-1.91 (1H, m), 2.30-2.40 (2H, m), 2.60-2.73 (2H, m), 2.81-2.94 (2H, m), 3.06-3.23 (1H, m), 3.54-3.64 (3H, m), 3.68-3.79 (2H, m), 4.01-4.12 (3H, m), 4.17 (2H, q, J=7.1Hz), 4.51 (2H, s), 7.26-7.36 (5H, m)

MASS (m/z) : 588 (M^++1)

Example 70

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-propanoyl]-3-piperidylcarbonyl]-2-hydroxymethyl-β-alanine ethyl ester

IR (Film) : 2970, 2930, 2855, 1710, 1660, 1620 cm^{-1}

NMR ($CDCl_3$, δ) : 1.01-1.26 (2H, m), 1.28 (3H, t,

J=7.1Hz), 1.45 (9H, s), 1.53-1.78 (6H, m), 1.85-2.13 (3H, m), 2.32-2.40 (4H, m), 2.60-2.79 (3H, m), 3.24-3.96 (8H, m), 4.02-4.15 (2H, m), 4.17 (2H, q, J=7.1Hz), 6.29-6.40, 6.77-6.88 (total 1H, m)

MASS (m/z) : 498 (M^++1)

Example 71

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-propanoyl]-3-piperidylcarbonyl]-2-benzoylaminomethyl-β-alanine ethyl ester

IR (Film) : 3070, 2975, 2930, 2850, 1725, 1640 cm^{-1}

NMR ($CDCl_3$, δ) : 1.00-1.33 (3H, m), 1.30 (3H, t, J=7.1Hz), 1.45 (9H, s), 1.52-1.83 (7H, m), 1.90-2.12 (2H, m), 2.53-2.44 (3H, m), 2.60-2.73 (2H, m), 2.83-2.95 (1H, m), 3.12-3.41 (3H, m), 4.02-4.14 (6H, m), 4.20 (2H, q, J=7.1Hz), 6.92-7.04 (1H, m), 7.42-7.57 (4H, m), 7.83-7.86 (2H, m)

MASS (m/z) : 601 (M^++1)

Example 72

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-propanoyl]-3-piperidylcarbonyl]-2-acetylaminomethyl-β-alanine ethyl ester

IR (Film) : 2920, 2850, 1720, 1650 cm^{-1}

NMR ($CDCl_3$, δ) : 1.01-1.21 (2H, m), 1.28 (3H, t, J=7.1Hz), 1.45 (9H, s), 1.37-1.98 (11H, m), 2.02 (3H, s), 2.27-2.43 (3H, m), 2.62-2.84 (3H, m), 3.05-3.36 (3H, m), 3.73-4.23 (8H, m), 6.89-7.04 (1H, m)

MASS (m/z) : 539 (M^++1)

Example 73

A mixture of N-benzyl-3-cyclopropyl-β-alanine (1.35 g), 10% Pd-C (0.27 g) and ammonium formate (1.72 g) in

ethanol (15 ml) was hydrogenated at atmospheric pressure for 2 hours. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo. The residue, (R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidinecarboxylic acid (2 g) and 1-hydroxybenztriazole (0.74 g) was dissolved in dimethylformamide (20 ml), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1 ml) was added under stirring at 0°C. After stirring at ambient temperature for overnight, the mixture was poured into water. The whole was extracted with ethyl acetate, washed with aqueous saturated $NaHCO_3$, water, and brine, and dried over $MgSO_4$, and evaporated in vacuo, subsequently. The residue was purified by column chromatography on silica gel eluting with n-hexane:AcOEt = (1:2) to give N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3-cyclopropyl-β-alanine methyl ester as a colorless oil (2.58 g, 93.5%).

IR (Film) : 3300, 3080, 2980, 2930, 2960, 1725, 1650, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 0.20-0.57 (4H, m), 0.92-1.09 (1H, m), 1.22-1.57 (8H, m), 1.46 (9H, s), 1.69-1.81 (3H, m), 1.85-2.05 (1H, m), 2.21-2.39 (2H, m), 2.57-2.83 (4H, m), 3.25-3.73 (3H, m), 4.07-4.18 (5H, m), 6.23 (1H, d, J=15.3Hz), 6.82 (1H, dd, J=15.3 and 6.6Hz), 6.79-6.93 (1H, m)

MASS (m/z) : 506 (M^++1)

The following compound was obtained according to a similar manner to that of Example 73.

Example 74

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-propanoyl]-3-piperidylcarbonyl]-3-cyclopropyl-β-alanine ethyl ester

IR (Film) : 2980, 2920, 2850, 1715, 1650, 1620 cm^{-1}

NMR ($CDCl_3$, δ) : 0.20-0.57 (4H, m), 0.96-1.20 (2H, m), 1.23-1.31 (4H, m), 1.40-1.74 (9H, m), 1.45 (9H, s), 1.89-2.41 (4H, m), 2.56-2.75 (4H, m), 3.20-3.39 (1H, m), 3.49-3.65 (2H, m), 3.85-4.20 (5H, m), 6.50-6.84 (1H, m)

MASS (m/z) : 508 (M^++1)

Example 75

A solution of LiOH (0.11 g) in H_2O (10 ml) was added to a solution of N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(R)-(3,4-dimethoxyphenethyl)-β-alanine methyl ester (1.83 g) in tetrahydrofuran (10 ml)-EtOH (10 ml) at 0°C. The reaction mixture was stirred for 3 hours at room temperature, and the solvent was evaporated in vacuo. The residue was resolved in ethyl acetate-water, and acidified with 10% aq. $KHSO_4$. The whole was washed with water and brine, dried over $MgSO_4$, and evaporated in vacuo to give N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(R)-(3,4-dimethoxyphenethyl)-β-alanine as a colorless oil (1.33 g, 74.4%).

IR (Film) : 2980, 2930, 2850, 1720, 1645 cm^{-1}

NMR ($DMSO_3$, δ) : 1.18-1.33 (2H, m), 1.39 (9H, s), 1.64-1.91 (8H, m), 2.17-2.46 (5H, m), 2.57-3.19 (4H, m), 3.70 (3H, s), 3.73 (3H, s), 3.90-4.08 (5H, m), 4.17-4.46 (1H, m), 6.43 (1H, d, J=15.1Hz), 6.61 (1H, dd, J=15.1 and 6.4Hz), 6.45-6.85 (3H, m), 7.83 (1H, d, J=8.4Hz), 12.09 (1H, s)

MASS (m/z) : 602 (M^++1)

The following compounds [Examples 76 to 102] were obtained according to a similar manner to that of Example 75.

Example 76

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(R)-(4-methoxyphenethyl)-β-alanine

IR (Film) : 2950, 2890, 2820, 1690, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 1.18-1.47 (4H, m), 1.39 (9H, s), 1.60-1.95 (8H, m), 2.11-2.44 (5H, m), 2.57-2.84 (3H, m), 3.71 (3H, s), 3.90-4.08 (4H, m), 4.21-4.44 (1H, m), 6.43 (1H, d, J=15.2Hz), 6.66 (1H, dd, J=15.2 and 6.4Hz), 6.82 (2H, d, J=8.6Hz), 7.07 (2H, d, J=8.6Hz), 7.83 (1H, d, J=8.4Hz), 12.08 (1H, br)

MASS (m/z) : 572 (M^++1)

Example 77

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-methoxymethyl-β-alanine

IR (Film) : 3000, 2955, 2900, 1720, 1660 cm^{-1}

NMR (DMSO-d_6, δ) : 1.06-1.33 (2H, m), 1.39 (9H, s), 1.55-1.83 (7H, m), 2.15-2.41 (6H, m), 2.64-2.84 (2H, m), 3.23 (3H, s), 3.77-3.97 (4H, m), 4.11-4.40 (2H, m), 6.42 (1H, d, J=15.2Hz), 6.55-6.66 (1H, m), 7.84-7.93 (1H, m)

MASS (m/z) : 482 (M^++1)

Example 78

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3-cyclopropyl-β-alanine

IR (Film) : 3280, 2980, 2920, 2850, 1700, 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 0.08-0.43 (2H, m), 1.17-1.32 (2H, m), 1.29-1.85 (13H, m), 1.29 (9H, s), 2.11-2.45 (3H, m), 2.59-3.04 (2H, m), 3.51-3.70 (1H, m), 3.90-4.08 (3H, m), 6.43 (1H, d, J=15.2Hz), 6.60 (1H, dd, J=15.2 and 6.5Hz), 7.82 (1H, d, J=8.4Hz), 12.08 (1H, br)

MASS (m/z) : 478 (M^++1)

Example 79

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2-hydroxymethyl-β-alanine

IR (Film) : 3300, 2930, 2870, 1720, 1650, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 1.08-1.44 (6H, m), 1.39 (9H, s), 1.50-1.87 (5H, m), 2.11-2.40 (2H, m), 2.57-3.25 (5H, m), 3.53 (2H, d, J=5.7Hz), 3.90-4.01 (3H, m), 4.18-4.42 (1H, m), 6.40-6.68 (2H, m), 7.95-8.00 (1H, m)

MASS (m/z) : 468 (M^++1)

Example 80

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3-ethynyl-β-alanine

IR (Film) : 3270, 2925, 2855, 1720, 1650, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 1.17-1.32 (2H, m), 1.37 (9H, s), 1.39-1.86 (7H, m), 2.11-2.40 (2H, m), 2.55-3.11 (6H, m), 3.21 (1H, d, J=2.3Hz), 3.90-3.98 (2H, m), 4.13-4.45 (1H, m), 4.75-4.88 (1H, m), 6.42 (1H, d, J=15.3Hz), 6.60 (1H, dd, J=15.3 and 6.3Hz), 8.43 (1H, d, J=8.0Hz)

MASS (m/z) : 462 (M^++1)

Example 81

N-[(S)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3-ethynyl-β-alanine

IR (Film) : 3260, 2925, 2850, 1720, 1645 cm^{-1}

NMR (DMSO-d_6, δ) : 1.17-1.32 (2H, m), 1.39 (9H, s), 1.39-1.85 (6H, m), 2.10-2.40 (2H, m), 2.55-2.83 (6H, m), 3.21 (1H, d, J=2.3Hz), 3.91-4.01 (3H, m), 4.14-4.44 (1H, m), 4.76-4.89 (1H, m), 6.42 (1H, d, J=15.2Hz), 6.55-6.64 (1H, m), 8.42 (1H,

d, J=8.2Hz)

MASS (m/z) : 462 (M^++1)

Example 82

N-[1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-4-piperidylcarbonyl]-3(S)-ethynyl-β-alanine

IR (Film) : 3220, 2925, 2880, 1715, 1645, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 1.10-1.51 (4H, m), 1.39 (9H, s), 1.65-1.71 (4H, m), 2.23-2.43 (2H, m), 2.57 (2H, d, J=7.3Hz), 2.65-2.87 (3H, m), 2.93-3.10 (1H, m), 3.19 (1H, d, J=2.3Hz), 3.91-4.13 (3H, m), 4.28-4.41 (1H, m), 4.75-4.89 (1H, m), 6.42 (1H, d, J=15.2Hz), 6.61 (1H, dd, J=15.2 and 6.4Hz), 8.32 (1H, d, J=8.2Hz)

MASS (m/z) : 462 (M^++1)

Example 83

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-3-azetidinyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine

NMR ($CDCl_3$, δ) : 1.44 (9H, s), 1.45-2.20 (4H, m), 2.20-2.55 (2H, m), 2.55-2.90 (3H, m), 3.05-3.40 (3H, m), 3.40-4.05 (4H, m), 4.20-4.70 (1H, m), 5.00-5.20 (1H, m), 6.20-6.45 (1H, m), 6.60-7.20 (2H, m), 7.35-7.65 (1H, m)

MASS (m/z) : 334 (M^++1-Boc)

Example 84

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-methacryloyl]-3-piperidylcarbonyl]-3-(S)-ethynyl-β-alanine

IR (Neat) : 1730, 1650 cm^{-1}

NMR ($CDCl_3$, δ) : 1.10-1.40 (2H, m), 1.40-2.20 (7H, m), 1.49 (9H, s), 1.84 (3H, d, J=1.4Hz), 2.27 (1H, d, J=2.4Hz), 2.35-3.20 (7H, m), 3.85-4.20 (3H, m), 4.45-4.85 (1H, m), 4.95-5.15 (1H, m), 5.15-5.30 (1H, m)

Example 85

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3,3-dimethyl-β-alanine

IR (Film) : 1730, 1650 cm^{-1}

NMR ($CDCl_3$, δ) : 1.39 (6H, s), 1.46 (9H, s), 1.50-2.45 (11H, m), 2.45-3.05 (4H, m), 3.05-3.40 (1H, m), 3.60-4.70 (6H, m), 6.10-6.60 (1H, m), 6.60-6.95 (1H, m)

Example 86

N-[(R)-1-[2-(1-tert-Butoxycarbonyl-4-piperidyl)-(1R*,2S*)-cyclopropan-1-yl-carbonyl]-3-piperidylcarbonyl]-(3S)-ethynyl-β-alanine

IR (Neat) : 1720, 1650 cm^{-1}

NMR ($CDCl_3$, δ) : 0.50-1.35 (6H, m), 1.35-2.20 (10H, m), 1.45 (9H, s), 2.20-2.45 (2H, m), 2.45-3.10 (4H, m), 3.10-4.60 (7H, m), 4.95-5.20 (1H, m), 6.45-6.95 (1H, br)

MASS (m/z) : 476 (M^++1)

Example 87

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-3-methyl-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine

IR (Nujol) : 1660 cm^{-1}

NMR ($CDCl_3$, δ) : 1.15-1.60 (2H, m), 1.47 (9H, s), 1.60-2.45 (9H, m), 2.45-2.90 (5H, m), 2.90-3.25 (2H, m), 3.45-4.70 (6H, m), 4.90-5.20 (1H, m), 5.74 (1H, s)

MASS (m/z) : 476 (M^++1)

Example 88

3-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]aminobenzoic acid

IR (Film) : 3250, 3000, 2925, 2850, 1700, 1650 cm^{-1}

NMR (DMSO-d_6, δ) : 1.09-1.49 (3H, m), 1.39 (9H, s), 1.38-1.81 (4H, m), 1.91-2.03 (1H, m), 2.20-2.46 (2H, m), 2.64-2.86 (3H, m), 2.97-3.15 (1H, m), 3.87-4.11 (3H, m), 4.13-4.53 (1H, m), 6.43-6.69 (2H, m), 7.42 (1H, t, J=7.9Hz), 7.62 (1H, d, J=7.7Hz), 7.82 (1H, d, J=8.0Hz), 8.24 (1H, s), 10.17 (1H, s)

MASS (m/z) : 486 (M^++1)

Example 89

4-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]aminobenzoic acid

IR (Film) : 3000, 2925, 2850, 1700, 1670, 1650 cm^{-1}

NMR (DMSO-d_6, δ) : 1.14-1.49 (3H, m), 1.39 (9H, s), 1.39-1.80 (5H, m), 1.91-2.03 (1H, m), 2.22-2.37 (1H, m), 2.63-2.84 (3H, m), 2.97-3.21 (1H, m), 3.87-4.12 (3H, m), 4.18-4.35 (1H, m), 6.42-6.69 (2H, m), 7.71 (2H, d, J=8.7Hz), 7.79 (2H, d, J=8.7Hz), 10.29 (1H, s), 12.41-12.60 (1H, br)

MASS (m/z) : 486 (M^++1)

Example 90

2-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]aminobenzoic acid

IR (Film) : 3000, 2930, 2860, 1720, 1660, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 1.11-1.53 (5H, m), 1.39 (9H, s), 1.91-2.48 (4H, m), 2.60-3.10 (6H, m), 3.86-4.14 (4H, m), 6.46 (1H, d, J=7.1Hz), 6.55-6.69 (1H, m), 7.15 (1H, t, J=7.1Hz), 7.58 (1H, t, J=7.1Hz), 7.98 (1H, d, J=8.1Hz), 8.44 (1H, d, J=8.1Hz), 11.30 (1H, br)

MASS (m/z) : 486 (M^++1)

Example 91

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-

acryloyl]-3-piperidylcarbonyl]-2-benzyloxymethyl-β-alanine

IR (Film) : 3300, 2960, 2930, 2860, 1720, 1670, 1650 cm^{-1}

NMR (DMSO-d_6, δ) : 1.10-1.33 (2H, m), 1.39 (9H, s), 1.39-1.83 (8H, m), 2.12-2.40 (2H, m), 2.57-2.84 (4H, m), 3.20-3.30 (1H, m), 3.57 (2H, d, J=6.1Hz), 3.88-4.01 (3H, m), 4.18-4.41 (1H, m), 4.46 (2H, s), 6.42 (1H, d, J=15.2Hz), 6.60 (1H, dd, J=15.2 and 6.4Hz), 7.27-7.38 (5H, m), 7.93-8.00 (1H, m), 12.31 (1H, br)

MASS (m/z) : 558 (M^++1)

Example 92

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-benzoyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine

IR (Film) : 3380, 3000, 2930, 2860, 1720, 1650, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 1.33-1.99 (8H, m), 1.41 (9H, s), 2.24-2.80 (2H, m), 2.55-2.80 (6H, m), 3.19 (1H, d, J=2.3Hz), 3.40-3.63 (1H, m), 4.01-4.12 (2H, m), 4.27-4.45 (1H, m), 4.74-4.87 (1H, m), 7.13-7.21 (2H, m), 7.26-7.37 (2H, m), 8.33-8.46 (1H, m), 12.33-12.47 (1H, br)

MASS (m/z) : 512 (M^++1)

Example 93

N-[(R)-1-[4-(1-tert-Butoxycarbonyl-4-piperidyl)-benzoyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine

IR (Film) : 3350, 2925, 2850, 1720, 1655, 1605 cm^{-1}

NMR (DMSO-d_6, δ) : 1.41 (9H, s), 1.41-1.91 (10H, m), 2.22-2.40 (1H, m), 2.51-3.00 (7H, m), 3.18 (1H, d, J=2.3Hz), 4.01-4.12 (2H, m), 4.74-4.86 (1H, m), 7.30 (4H, s), 8.37-8.48 (1H, m), 12.35-12.41 (1H, br)

MASS (m/z) : 512 (M^++1)

Example 94

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-propanoyl]-3-piperidylcarbonyl]-3(S)-methoxymethyl-β-alanine

IR (Film) : 2950, 2900, 1730, 1660, 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 0.87-1.08 (2H, m), 1.38 (9H, s), 1.26-1.83 (9H, m), 2.11-2.41 (6H, m), 2.55-2.74 (2H, m), 2.84-3.14 (2H, m), 3.24 (3H, s), 3.71-3.95 (4H, m), 4.13-4.35 (2H, m), 7.82-7.91 (1H, m), 12.06-12.29 (1H, br)

MASS (m/z) : 384(M^+-Boc+1)

Example 95

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-propanoyl]-3-piperidylcarbonyl]-3-cyclopropyl-β-alanine

IR (Film) : 3400, 3000, 2910, 2855, 1700, 1640, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 0.11-0.46 (4H, m) 0.84-1.08 (3H, m), 1.23-1.44 (5H, m), 1.38 (9H, s), 1.53-1.82 (5H, m), 2.11-2.45 (5H, m), 2.51-2.75 (2H, m), 2.86-3.09 (1H, m), 3.56-3.80 (2H, m), 3.86-3.97 (2H, m), 4.13-4.39 (1H, m), 7.80-7.90 (1H, m)

MASS (m/z) : 480 (M^++1)

Example 96

3-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-propanoyl]-3-piperidylcarbonyl]aminobenzoic acid

IR (Film) : 3260, 3000, 2930, 2850, 1700, 1660, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 0.84-1.07 (1H, m), 1.39 (9H, s), 1.37-1.50 (4H, m), 1.60-1.80 (5H, m), 1.91-1.99 (1H, m), 2.31-2.41 (2H, m), 2.51-2.79 (4H, m), 2.93-3.31 (1H, m), 3.79-4.00 (3H, m), 4.12-4.51 (1H, m), 7.42 (1H, d, J=7.6Hz), 7.62 (1H, d, J=7.6Hz), 7.76-7.85 (1H, m), 8.23 (1H, s), 10.16

(1H, d, J=3.7Hz)

MASS (m/z) : 388 (M^+-Boc+1)

Example 97

4-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-propanoyl]-3-piperidylcarbonyl]aminobenzoic acid

IR (Film) : 2930, 2850, 1760, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 0.87-1.05 (1H, m), 1.38 (9H, s), 1.37-1.50 (5H, m), 1.60-1.80 (4H, m), 1.91-2.04 (1H, m), 2.31-2.40 (2H, m), 2.51-2.79 (4H, m), 2.95-3.22 (1H, m), 3.77-3.96 (3H, m), 4.12-4.49 (1H, m), 7.70 (2H, d, J=8.0Hz), 7.89 (2H, d, J=8.4Hz), 10.28 (1H, s)

MASS (m/z) : 388 (M^+-Boc+1)

Example 98

2-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-propanoyl]-3-piperidylcarbonyl]aminobenzoic acid

IR (Film) : 2925, 2855, 1720, 1660, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 0.83-1.09 (2H, m), 1.38 (9H, s), 1.38-1.78 (6H, m), 1.99-2.16 (1H, m), 2.26-2.41 (3H, m), 2.58-3.06 (5H, m), 3.68-4.56 (6H, m), 7.15 (1H, t, J=7.4Hz), 7.51-7.60 (1H, m), 7.9 (1H, d, J=8.9Hz), 8.41 (1H, t, J=7.3Hz)

MASS (m/z) : 488 (M^++1)

Example 99

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-propanoyl]-3-piperidylcarbonyl]-2-benzyloxymethyl-β-alanine

IR (Film) : 3400, 2930, 2855, 1720, 1660, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 0.83-1.09 (2H, m), 1.23-1.49 (8H, m), 1.38 (9H, s), 1.52-1.85 (4H, m), 2.25-2.37 (2H, m), 2.57-2.77 (4H, m), 2.93-3.11 (1H, m), 3.55-3.62 (2H, m), 3.69-3.97 (3H, m), 4.18-4.40

(1H, m), 4.46 (2H, s), 7.26-7.37 (5H, m), 7.89-7.99 (1H, m)

MASS (m/z) : 560 (M^++1)

Example 100

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-propanoyl]-3-piperidylcarbonyl]-2-hydroxymethyl-β-alanine

IR (Film) : 2930, 2860, 1720, 1660, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86-1.08 (2H, m), 1.38 (9H, s), 1.58-1.85 (11H, m), 2.13-2.37 (3H, m), 2.51-3.25 (5H, m), 3.53 (2H, d, J=5.1Hz), 3.71-3.96 (4H, m), 4.13-4.39 (1H, m),7.94-8.03 (1H, m)

MASS (m/z) : 470 (M^++1)

Example 101

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-propanoyl]-3-piperidylcarbonyl]-2-benzoylaminomethyl-β-alanine

IR (Film) : 3280, 3050, 2920, 2850, 1710, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 0.84-1.05 (2H, m), 1.38 (9H, s), 1.35-1.46 (4H, m), 1.60-1.70 (4H, m), 1.76-1.86 (1H, m), 2.27-2.38 (2H, m), 2.51-3.15 (6H, m), 3.24-3.52 (4H, m), 3.74-3.95 (3H, m), 4.13-4.40 (1H, m), 7.43-7.54 (3H, m), 7.81-7.84 (2H, m), 8.00-8.11 (1H, m), 8.51-8.60 (1H, m)

MASS (m/z) : 573 (M^++1)

Example 102

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-propanoyl]-3-piperidylcarbonyl]-2-acetylaminomethyl-β-alanine

IR (Film) : 3325, 2920, 2850, 1720, 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86-4.08 (2H, m), 1.17 (9H, s), 1.17-1.47 (4H, m), 1.60-1.71 (5H, m), 1.91 (3H, s), 2.28-2.40 (2H, m), 2.51-2.94 (6H, m), 3.14-

3.44 (4H, m), 3.76-4.39 (4H, m), 7.89-8.03 (2H, m)

MASS (m/z) : 511 (M^++1)

Example 103

To a mixture of N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine (0.6 g), n-pentylalcohol (0.16 ml) and N,N-dimethylaminopyridine (16 mg) in dichloromethane (6 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (0.27 g) at 0°C. After stirring at room temperature for overnight, the solution was evaporated in vacuo. The residue was poured into water and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogencarbonate, water and brine, dried over $MgSO_4$, and evaporated in vacuo, subsequently. The residue was purified by column chromatography on silica gel eluting with AcOEt:Hexane = (1:1) to give N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine n-pentyl ester as a colorless oil (0.65 g, 94.0%).

IR (Film) : 2900, 2825, 1710, 1640, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 0.89-0.97 (3H, m), 1.26-1.40 (7H, m), 1.46 (9H, s), 1.61-1.79 (6H, m), 1.92-2.05 (1H, m), 2.28 (1H, d, J=2.3Hz), 2.24-2.38 (2H, m), 2.68-2.83 (4H, m), 3.23-3.39 (2H, m), 3.64-4.26 (6H, m), 5.05-5.16 (1H, m), 6.22 (1H, d, J=15.2Hz), 6.82 (1H, dd, J=15.2 and 6.6Hz), 7.07-7.16 (1H, m)

MASS (m/z) : 532 (M^++1)

The following compounds [Examples 104 to 107] were obtained according to a similar manner to that of Example 103.

Example 104

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine n-butyl ester

NMR ($CDCl_3$, δ) : 0.96 (3H, t, J=7.3Hz), 1.33 (2H, d, J=7.3Hz), 1.36-1.45 (3H, m), 1.46 (9H, s), 1.56-1.77 (4H, s), 1.90-2.05 (2H, m), 2.20-2.31 (2H, m), 2.28 (1H, d, J=2.4Hz), 2.60-2.81 (4H, m), 4.06-4.18 (5H, m), 5.05-5.13 (1H, m), 6.23 (1H, d, J=15.1Hz), 6.82 (1H, dd, J=6.7 and 15.1Hz)

MASS (m/z) : 518 (M^++1)

Example 105

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine phenethyl ester

IR (Film) : 2930, 2850, 1730, 1650, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.26-1.40 (2H, m), 1.46 (9H, s), 1.45-1.89 (8H, m), 1.95-2.04 (1H, m), 2.20-2.39 (1H, m), 2.25 (1H, d, J=2.4Hz), 2.67-2.91 (4H, m), 2.97 (2H, t, J=7.0Hz), 3.20-3.41 (1H, m), 4.07-4.17 (3H, m), 4.36 (2H, t, J=7.0Hz), 5.01-5.13 (1H, m), 6.23 (1H, d, J=15.2Hz), 6.82 (1H, dd, J=15.2 and 6.7Hz), 7.21-7.51 (6H, m)

MASS (m/z) : 566 (M^++1)

Example 106

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-β-alanine n-butyl ester

IR (Film) : 2920, 2855, 1725, 1680, 1650, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 0.94 (3H, t, J=7.2Hz), 1.27-1.79 (12H, m), 1.46 (9H, s), 1.90-2.01 (1H, m), 2.23-2.36 (2H m), 2.52 (2H, t, J=6.1Hz), 2.70-2.81 (2H, m), 3.29 (1H, dd, J=13.5 and 9.3Hz), 3.65-3.76 (3H, m), 4.10 (2H, t, J=6.6Hz), 4.00-4.20

(3H, m), 6.22 (1H, d, J=15.2Hz), 6.55-6.68 (1H, m), 681 (1H, dd, J=15.2 and 6.7Hz)

MASS (m/z) : 494 (M^++1)

Example 107

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)propanoyl]-3-piperidylcarbonyl]-2(S)-acetylamino-β-alanine n-pentyl ester

IR (Film) : 2910, 2850, 1720, 1640 cm^{-1}

NMR ($CDCl_3$, δ) : 0.91 (3H, t, J=6.6Hz), 1.00-1.22 (2H, m), 1.31-1.36 (4H, m), 1.45 (9H, s), 1.40-1.77 (13H, m), 2.04-2.09 (3H, m), 2.34-2.51 (3H, m), 2.60-2.74 (2H, m), 3.20-3.49 (2H, m), 3.57-3.75 (2H, m), 4.02-4.25 (5H, m), 4.57-4.80 (1H, m), 6.88-7.20 (1H, m)

MASS (m/z) : 467 (M^+-Boc+1)

Example 108

To a solution of N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine (0.5 g) in dimethylformamide (5 ml) was added K_2CO_3 (75 mg) under stirring at 0°C, stirred for 15 minutes, and pivalic acid iodomethyl ester (0.61 g) in dimethylformamide (3 ml) was added to the mixture. After stirring at room temperature for 1 hour, the mixture was poured into water and extracted with ethyl acetate. The extract was washed with water and brine, dried over $MgSO_4$, and evaporated in vacuo, subsequently. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$:MeOH = (98:2) to give N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine pivaloyloxymethyl ester as a colorless oil (0.37 g, 59.3%).

IR (Film) : 2960, 2920, 2850, 1745, 1650, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.22 (9H, s), 1.32-1.60 (3H, m), 1.46 (9H, s), 1.69-1.80 (3H, m), 1.89-2.03 (2H, m), 2.16-2.40 (5H, m), 2.28 (1H, d, J=2.4Hz), 2.70-2.85 (4H, m), 3.33-3.51 (1H, m), 4.04-4.18 (3H, m), 5.04-5.17 (1H, m), 5.77 (2H, s), 6.24 (1H, d, J=15.1Hz), 6.83 (1H, dd, J=15.1 and 6.6Hz)

MASS (m/z) : 576 (M^++1)

The following compound was obtained according to a similar manner to that of Example 108.

Example 109

N-[(R)-1-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-β-alanine pivaloyloxymethyl ester

IR (Film) : 2960, 2930 2855, 1750, 1670, 1650, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.21 (9H, s), 1.21-2.05 (8H, m), 1.46 (9H, s), 2.21-2.39 (2H, m), 2.58 (2H, t, J=6.1Hz), 2.70-2.83 (2H, m), 3.23-3.78 (5H, m), 4.07-4.20 (3H, m), 5.76 (2H, d, J=2.4Hz), 6.22 (1H, d, J=15.2Hz), 6.65-6.79 (1H, m), 6.81 (1H, dd, J=15.2 and 6.7Hz)

MASS (m/z) : 552 (M^++1)

Example 110

To a solution of N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2-hydroxymethyl-β-alanine (0.24 g) in ethyl acetate (2 ml) was added 4N HCl in ethyl acetate (1.3 ml) at 0°C, and the reaction mixture was stirred for 2 hours at room temperature. The precipitates were filtered and washed with diethyl ether to give N-[(R)-1-[3-(4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2-hydroxymethyl-β-alanine hydrochloride (0.17 g, 82.0%).

IR (KBr pellet) : 3440, 2947, 2866, 1728, 1659 cm^{-1}

NMR (D_2O, δ) : 1.40-1.83 (7H, m), 1.92-2.08 (4H, m), 2.40-2.69 (4H, m), 2.78-2.92 (2H, m), 2.99-3.29 (3H, m), 3.38-3.55 (3H, m), 3.78 (2H, d, J=5.9Hz), 3.92-4.18 (1H, m), 4.25-4.37 (1H, m), 6.46 (1H, dd, J=15.8Hz), 6.58-6.71 (1H, m)

MASS (m/z) : 368 (M^+free+1)

The following compounds [Examples 111 to 124] were obtained according to a similar manner to that of Example 110.

Example 111

N-[1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine hydrochloride

IR (KBr pellet) : 2954, 2729, 2360, 2337, 1724, 1655 cm^{-1}

NMR (D_2O, δ) : 1.52-1.75 (4H, m), 1.84-1.93 (2H, m), 2.01-2.07 (2H, m), 2.51-2.68 (2H, m), 2.74 (1H, d, J=2.3Hz), 2.85 (2H, dd, J=7.0 and 2.9Hz), 3.00-3.25 (3H, m), 3.40-3.51 (2H, m), 4.08-4.20 (1H, m), 4.39-4.49 (1H, m), 4.64-4.98 (3H, m), 6.46 (1H, d, J=15.6Hz), 6.64 (1H, dd, J=15.6 and 6.2Hz)

MASS (m/z) : 362 (M^+free+1)

$[\alpha]_D^{25}$ = -37.97° (C=1.0, MeOH)

Example 112

3-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]aminobenzoic acid hydrochloride

IR (KBr pellet) : 2951, 2862, 2729, 1711, 1655 cm^{-1}

NMR (D_2O, δ) : 1.50-2.10 (10H, m), 2.36-2.76 (2H, m), 2.91-3.70 (5H, m), 3.84-4.49 (2H, m), 6.46 (1H, dd, J=15.5 and 2.2Hz), 6.56-6.72 (1H, m), 7.48 (1H, td, J=7.9 and 2.2Hz), 7.66 (1H, d,

J=8.3Hz), 7.79 (1H, d, J=6.6Hz), 8.01 (1H, d, J=1.8Hz)

MASS (m/z) : 386 (M^+free+1)

Example 113

4-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]aminobenzoic acid hydrochloride

IR (KBr pellet) : 3425, 2947, 2862, 2729, 1691, 1655 cm^{-1}

NMR (D_2O, δ) : 1.47-2.10 (8H, m), 2.29-2.79 (3H, m), 2.89-4.46 (8H, m), 6.39-6.72 (2H, m), 7.56 (2H, d, J=8.7Hz), 7.97 (2H, dd, J=8.8 and 2.1Hz)

MASS (m/z) : 386 (M^+free+1)

$[\alpha]_D^{25}$ = -34.70° (C=1.0, MeOH)

Example 114

2-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]aminobenzoic acid hydrochloride

IR (KBr pellet) : 3425, 2947, 2862, 2821, 2727, 1682, 1657 cm^{-1}

NMR (D_2O, δ) : 1.51-2.16 (9H, m), 2.40-2.80 (2H, m), 2.95-3.50 (6H, m), 3.62-4.08 (2H, m), 6.44-6.69 (2H, m), 7.26-7.36 (1H, m), 7.53-7.66 (1H, m), 7.87-8.03 (2H, m)

MASS (m/z) : 386 (M^+free+1)

$[\alpha]_D^{25}$ = -7.53° (C=1.0, MeOH)

Example 115

N-[(R)-1-[3-(4-Piperidyl)benzoyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine

IR (KBr pellet) : 2721, 1728, 1655, 1599, 1579 cm^{-1}

NMR (D_2O, δ) : 1.32-1.47 (1H, m), 1.54-1.99 (8H, m), 2.33-2.46 (1H, m), 2.54-2.65 (3H, m), 2.80-3.07 (5H, m), 3.19 (1H, d, J=2.0Hz), 3.30-3.40 (2H, m), 4.32-4.44 (1H, m), 4.73-4.87 (1H, m), 7.21-

7.45 (4H, m), 8.49-8.57 (1H, m)

MASS (m/z) : 412 (M^+free+1)

$[\alpha]_D^{25}$ = -40.47° (C=1.0, MeOH)

Example 116

N-[(R)-1-[4-(4-Piperidyl)benzoyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine

IR (KBr pellet) : 2929, 1728, 1649, 1605 cm^{-1}

NMR (D_2O, δ) : 1.30-1.97 (9H, m), 2.25-2.41 (1H, m), 2.54-2.64 (2H, m), 2.82-3.08 (5H, m), 3.19 (1H, d, J=2.3Hz), 3.29-3.41 (2H, m), 4.24-4.44 (1H, m), 4.75-4.87 (1H, m), 7.29 (2H, d, J=8.3Hz), 7.35 (2H, d, J=8.3Hz), 8.43-8.51 (1H, m), 8.95-9.11 (2H, br)

MASS (m/z) : 412 (M^+free+1)

$[\alpha]_D^{25}$ = 49.77° (C=1.0, MeOH)

Example 117

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine phenethyl ester hydrochloride

IR (KBr pellet) : 3412, 3278, 3028, 2951, 2864, 2725, 1734, 1655 cm^{-1}

NMR (D_2O, δ) : 1.46-2.27 (9H, m), 2.41-3.43 (12H, m), 3.56-3.72 (2H, m), 4.10-4.64 (4H, m), 6.53-6.88 (2H, m), 7.25-7.35 (5H, m)

MASS (m/z) : 466 (M^+free+1)

Example 118

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-β-alanine n-butyl ester hydrochloride

IR (KBr pellet) : 3415, 3059, 2956, 2870, 2725, 1730, 1653 cm^{-1}

NMR (D_2O, δ) : 0.90 (3H, t, J=7.3Hz), 1.25-1.85 (10H, m), 1.93-2.09 (3H, m), 2.39-2.69 (2H, m),

2.57 (2H, t, J=6.4Hz), 2.92-3.27 (2H, m), 3.10 (2H, td, J=12.7 and 2.8Hz), 3.32-3.53 (4H, m), 3.93-4.40 (2H, m), 4.12 (2H, t, J=6.5Hz), 6.48 (1H, d, J=15.5Hz), 6.66 (1H, dd, J=15.5 and 6.2Hz)

MASS (m/z) : 394 (M^+free+1)

Example 119

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-β-alanine 1-(cyclohexyloxycarbonyl)-ethyl ester hydrochloride

IR (KBr pellet) : 3425, 3377, 3271, 3070, 2941, 2862, 2810, 2729, 1757, 1653 cm^{-1}

NMR (D_2O, δ) : 1.19-2.08 (18H, m), 1.50 (3H, d, J=5.3Hz), 2.34-2.62 (5H, m), 2.80-2.93 (1H, m), 3.03-3.15 (3H, m), 3.25-3.63 (4H, m), 4.00-4.49 (2H, m), 4.56-4.66 (1H, m), 6.49 (1H, d, J=15.6Hz), 6.66 (1H, dd, J=15.6 and 6.2Hz), 6.61-6.71 (1H, m)

MASS (m/z) : 508 (M^+free+1)

Example 120

(-)-N-[(R)-1-[3-(4-Piperidyl)propanoyl]-3-piperidylcarbonyl]-3-cyclopropyl-β-alanine hydrochloride

IR (KBr pellet) : 3444, 3392, 3076, 3008, 2949, 2866, 2731, 1732, 1716, 1649, 1622 cm^{-1}

NMR (D_2O, δ) : 0.24-0.34 (2H, m), 0.93-1.09 (1H, m), 1.36-1.84 (9H, m), 1.91-2.03 (3H, m), 2.32-2.82 (9H, m), 2.92-3.03 (3H, m), 3.11-3.46 (2H, m), 3.53-3.65 (1H, m), 3.76-3.93 (1H, m), 4.08-4.27 (1H, m)

MASS (m/z) : 380 (M^+free+1)

Example 121

3-[(R)-1-[3-(4-Piperidyl)propanoyl]-3-

piperidylcarbonyl]aminobenzoic acid hydrochloride

IR (KBr pellet) : 3444, 2949, 2866, 2731, 1713, 1684, 1653, 1614 cm^{-1}

NMR (D_2O, δ) : 1.23-1.69 (7H, m), 1.81-2.11 (6H, m), 2.42-2.75 (3H, m), 2.85-3.31 (3H, m), 3.37-3.56 (2H, m), 3.79-4.36 (2H, m), 7.48 (1H, td, J=7.9 and 2.9Hz), 7.64-7.69 (1H, m), 7.76-7.80 (1H, m), 8.02 (1H, s)

MASS (m/z) : 388 (M^++1)

Example 122

4-[(R)-1-[3-(4-Piperidyl)propanoyl]-3-piperidylcarbonyl]aminobenzoic acid hydrochloride

IR (KBr pellet) : 3101, 2947, 2862, 1691 cm^{-1}

NMR (D_2O, δ) : 1.28-1.69 (6H, m), 1.77-2.09 (5H, m), 2.40-2.78 (4H, m), 2.84-2.98 (2H, m), 3.11-3.46 (4H, m), 3.78-4.31 (2H, m), 7.58 (2H, dd, J=8.7 and 1.4Hz), 8.00 (2H, dd, J=8.7 and 1.8Hz)

MASS (m/z) : 388 (M^+free+1)

$[\alpha]_D^{25}$ = -24.4° (C=1.0, MeOH)

Example 123

2-[(R)-1-[3-(4-Piperidyl)propanoyl]-3-piperidylcarbonyl]aminobenzoic acid hydrochloride

IR (KBr pellet) : 3417, 2947, 2862, 2731, 1686, 1609 cm^{-1}

NMR (D_2O, δ) : 1.28-2.09 (11H, m), 2.49-2.76 (2H, m), 2.86-3.49 (6H, m), 3.51-4.40 (4H, m), 7.30 (1H, t, J=7.5Hz), 7.62 (1H, t, J=7.9Hz), 7.89-8.02 (2H, m)

MASS (m/z) : 388 (M^+free+1)

$[\alpha]_D^{25}$ = -8.85° (C=1.0, MeOH)

Example 124

N-[(R)-1-[3-(4-Piperidyl)propanoyl]-3-

piperidylcarbonyl]-2-hydroxymethyl-β-alanine hydrochloride

IR (KBr pellet) : 3419, 3064, 2945, 2866, 1726, 1643, 1620 cm^{-1}

NMR (D_2O, δ) : 1.36-2.09 (13H, m), 2.38-2.53 (3H, m), 2.81-3.03 (4H, m), 3.12-3.52 (5H, m), 3.78 (2H, d, J=5.9Hz), 3.86-3.93 (1H, m), 4.11-4.30 (1H, m)

MASS (m/z) : 370 (M^++1)

Example 125

To a solution of N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(R)-(3,4-dimethoxyphenethyl)-β-alanine (1.33 g) in ethyl acetate (10 ml) was added 4N HCl in 1,4-dioxane (5.53 ml) at 0°C, and the reaction mixture was stirred for 3 hours at room temperature. The precipitates were filtered, washed with diethyl ether and resolved in water, neutralized with saturated aqueous $NaHCO_3$, desalted by using the resin of HP-20 eluting with isopropanol:H_2O = (1:1), then freeze-dried to give N-[(R)-1-[3-(4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(R)-(3,4-dimethoxyphenethyl)-β-alanine as a white powder (0.88 g, 79.4%)

IR (Nujol) : 3400, 1635, 1600 cm^{-1}

NMR (D_2O, δ) : 1.41-2.05 (10H, m), 2.18-2.68 (4H, m), 2.40 (2H, d, J=7.3Hz), 2.97-3.12 (4H, m), 3.23-3.50 (3H, m), 3.82 (3H, s), 3.85 (3H, s), 3.87-4.20 (3H, m), 6.38-6.68 (2H, m), 6.80-6.98 (3H, m)

MASS (m/z) : 502 (M^++1)

$[\alpha]_D^{20}$ = -48.7° (C=1.0, MeOH)

The following compounds [Examples 126 to 143] were obtained according to a similar manner to that of Example 125.

Example 126

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(R)-(4-methoxyphenethyl)-β-alanine

IR (Nujol) : 3445, 1645, 1600 cm^{-1}

NMR (D_2O, δ) : 1.41-2.05 (10H, m), 2.18-2.68 (4H, m), 2.40 (2H, d, J=7.3Hz), 2.97-3.12 (4H, m), 3.23-3.50 (3H, m), 3.82 (3H, s), 3.85 (3H, s), 3.87-4.20 (3H, m), 6.38-6.68 (2H, m), 6.80-6.98 (3H, m)

MASS (m/z) : 472 (M^++1)

Elemental Analysis Calcd. for $C_{26}H_{37}N_3O_5 \cdot 0.3H_2O$: C 65.47, H 7.94, N 8.81

Found : C 65.36, H 7.92, N 8.92

Example 127

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-methoxymethyl-β-alanine

IR (KBr pellet) : 2939, 2862, 1652 cm^{-1}

NMR (D_2O, δ) : 1.45-1.88 (6H, m), 1.93-2.12 (3H, m), 2.26-2.67 (4H, m), 2.92-3.23 (3H, m), 3.36 (3H, s), 3.31-3.49 (4H, m), 3.90-4.20 (2H, m), 4.27-4.39 (2H, m), 6.47 (1H, d, J=15.7Hz), 6.59-6.72 (1H, m)

MASS (m/z) : 382 (M^++1)

Example 128

(-)-N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3-cyclopropyl-β-alanine

IR (KBr pellet) : 3444, 3392, 3082, 3012, 2949, 2862, 1653 cm^{-1}

NMR (D_2O, δ) : 0.20-0.32 (2H, m), 0.39-0.59 (2H, m), 0.93-1.01 (1H, m), 1.45-2.08 (9H, m), 2.40-2.67 (4H, m), 2.96-3.65 (7H, m), 3.88-4.27 (2H, m), 6.48 (1H, d, J=15.7Hz), 6.65 (1H, dt, J=15.7 and 5.89Hz)

MASS (m/z) : 378 (M^++1)

$[\alpha]_D^{20}$ = -73.6° (C=1.0, MeOH)

Elemental Analysis Calcd. for $C_{20}H_{31}N_3O_4 \cdot 0.2H_2O$:
C 58.09, H 8.53, N 10.16

Found : C 58.32, H 8.45, N 10.16

(+)-N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3-cyclopropyl-β-alanine

IR (KBr pellet) : 3471, 3412, 3365, 3802, 3007, 2949, 2862, 1653 cm^{-1}

NMR (D_2O, δ) : 0.18-0.35 (2H, m), 0.38-0.58 (2H, m), 0.90-1.08 (1H, m), 1.42-2.12 (9H, m), 2.33-2.69 (4H, m), 3.01-3.66 (7H, m), 4.00-4.32 (2H, m), 6.47 (1H, d, J=15.6Hz), 6.59-6.72 (1H, m)

MASS (m/z) : 378 (M^++1)

$[\alpha]_D^{20}$ = -38.5° (C=1.0, MeOH)

Elemental Analysis Calcd. for $C_{20}H_{31}N_3O_4 \cdot 2.3H_2O$:
C 57.34, H 8.57, N 10.03

Found : C 57.26, H 8.73, N 9.86

Example 129

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(R)-ethynyl-β-alanine

IR (KBr pellet) : 3415, 3271, 3051, 2947, 2860, 2748, 1655 cm^{-1}

NMR (D_2O, δ) : 1.41-1.87 (6H, m), 1.95-2.09 (3H, m), 2.39-2.70 (5H, m), 3.02-3.29 (4H, m), 3.40-3.50 (3H, m), 3.92-4.34 (2H, m), 6.47 (1H, d, J=15.6Hz), 6.59-6.71 (1H, m)

MASS (m/z) : 362 (M^++1)

$[\alpha]_D^{25}$ = -29.27° (C=1.0, MeOH)

Elemental Analysis Calcd. for $C_{19}H_{27}N_3O_4 \cdot 1.5H_2O$:
C 58.75, H 7.78, N 10.82

Found : C 58.79, H 7.96, N 10.56

Example 130

N-[(S)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine

IR (KBr pellet) : 3444, 3275, 2947, 2862, 1653 cm^{-1}

NMR (D_2O, δ) : 1.43-1.85 (6H, m), 1.93-2.10 (3H, m), 2.42-2.70 (5H, m), 3.03-3.51 (7H, m), 3.90-4.36 (2H, m), 6.48 (1H, d, J=15.6Hz), 6.59-6.72 (1H, m)

MASS (m/z) : 362 (M^++1)

$[\alpha]_D^{25}$ = 25.4° (C=1.0, MeOH)

Elemental Analysis Calcd. for $C_{19}H_{27}N_3O_4 \cdot 1.9H_2O$:
C 57.68, H 7.85, N 10.62

Found : C 57.61, H 8.10, N 10.41

N-[(S)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(R)-ethynyl-β-alanine

IR (KBr pellet) : 3439, 3259, 3049, 2945, 2860, 1655 cm^{-1}

NMR (D_2O, δ) : 1.41-1.89 (6H, m), 1.99-2.09 (3H, m), 2.39-2.67 (5H, m), 3.01-3.15 (3H, m), 3.17-3.50 (4H, m), 3.92-4.37 (2H, m), 6.46 (1H, d, J=15.7Hz), 6.59-6.67 (1H, m)

MASS (m/z) : 362 (M^++1)

$[\alpha]_D^{25}$ = 79.23° (C=1.0, MeOH)

Elemental Analysis Calcd. for $C_{19}H_{27}N_3O_4 \cdot 1.6H_2O$:
C 58.21, H 7.82, N 10.72

Found : C 58.35, H 8.23, N 10.48

Example 131

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2-benzyloxymethyl-β-alanine

IR (KBr pellet) : 3514, 3433, 3317, 3265, 2939, 2860, 1657 cm^{-1}

NMR (D_2O, δ) : 1.37-2.09 (8H, m), 2.26-2.43 (1H, m), 2.45-2.63 (1H, m), 2.69-2.81 (1H, m), 2.85-3.28

(4H, m), 3.35-3.50 (4H, m), 3.56-3.78 (2H, m), 3.85-4.00 (1H, m), 4.08-4.33 (2H, m), 4.55 (2H, s), 6.35-6.70 (2H, m), 7.44 (5H, s)

MASS (m/z) : 458 (M^++1)

Example 132

N-[(R)-1-[3-(4-Piperidyl)-(E)-methacryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine

IR (Nujol) : 1750, 1670 cm^{-1}

NMR (D_2O, δ) : 1.05-1.90 (8H, m), 1.56 (3H, s), 2.05-3.05 (8H, m), 2.37 (1H, d, J=2.2Hz), 3.05-3.25 (2H, m), 3.35-3.80 (2H, m), 3.80-4.05 (1H, m), 5.13 (1H, d, J=7.6Hz)

MASS (m/z) : 376 (M^++1)

Example 133

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3,3-dimethyl-β-alanine

NMR ($CDCl_3$, δ) : 1.25-2.15 (12H, m), 1.39 (6H, s), 2.20-2.60 (5H, m), 2.75-3.10 (3H, m), 3.10-3.55 (3H, m), 3.75-4.00 (1H, m), 4.05-4.35 (1H, m)

MASS (m/z) : 368 (M^++1)

Example 134

N-[(R)-1-[2-(4-Piperidyl)-(1R*,2S*)-cyclopropan-1-yl-carbonyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine

IR (Nujol) : 1600 cm^{-1}

NMR (D_2O, δ) : 0.45-0.70 (1H, m), 0.70-1.05 (3H, m), 1.05-1.85 (9H, m), 1.85-2.45 (4H, m), 2.45-2.75 (3H, m), 2.75-3.05 (1H, m), 3.05-3.25 (3H, m), 3.70-4.10 (2H, m)

MASS (m/z) : 376 (M^++1)

Example 135

N-[(R)-3-(4-Piperidyl)-3-methyl-(E)-acryloyl]-3-

piperidylcarbonyl]-3(S)-ethynyl-β-alanine

IR (Nujol) : 1640 cm^{-1}

NMR (D_2O, δ) : 1.35-2.15 (9H, m), 1.76 (3H, s), 2.20-2.55 (2H, m), 2.55-2.75 (3H, m), 2.85-3.60 (6H, m), 3.65-4.00 (1H, m), 4.05-4.35 (1H, m), 5.88 (1H, m)

MASS (m/z) : 376 (M^++1)

Example 136

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester

IR (KBr pellet) : 3427, 3269, 3049, 2941, 2862, 2742, 1732, 1655 cm^{-1}

NMR (D_2O, δ) : 1.10 (3H, t, J=7.2Hz), 1.32-1.68 (6H, m), 1.75-1.89 (3H, m), 2.23-2.54 (3H, m), 2.59-3.14 (6H, m), 3.23-3.30 (3H, m), 3.37-4.19 (2H, m), 4.03 (2H, q, J=7.2Hz), 4.76-4.86 (1H, m), 6.30 (1H, d, J=15.6Hz), 6.43-6.57 (1H, m)

MASS (m/z) : 390 (M^++1)

Elemental Analysis Calcd. for $C_{21}H_{31}N_3O_4 \cdot 2.7H_2O$: C 57.57, H 8.37, N 9.59

Found : C 57.89, H 8.13, N 9.19

Example 137

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine n-butyl ester

NMR (D_2O, δ) : 0.92 (3H, t, J=7.2Hz), 1.24-1.41 (5H, m), 1.59-1.76 (2H, m), 2.18-2.30 (2H, m), 2.58-2.82 (5H, m), 3.11-3.18 (2H, m), 3.83 (2H, d, J=7.2Hz), 5.16-5.19 (1H, m), 6.15 (1H, d, J=15.4Hz), 6.25-6.40 (1H, m)

MASS (m/z) : 418 (M^++1)

Example 138

N-[(R)-1-[3-(4-Piperidyl)propanoyl]-3-

piperidylcarbonyl]-2-benzyloxymethyl-β-alanine

IR (KBr pellet) : 3398, 2937, 2862, 1635 cm^{-1}

NMR (D_2O, δ) : 1.25-2.00 (12H, m), 2.24-2.50 (3H, m), 2.69-3.03 (4H, m), 3.08-3.32 (1H, m), 3.32-3.47 (4H, m), 3.56-3.88 (3H, m), 4.11-4.27 (1H, m), 4.50 (2H, s), 7.42 (5H, s)

MASS (m/z) : 460 (M^++1)

Example 139

N-[(R)-1-[3-(4-Piperidyl)propanoyl]-3-piperidylcarbonyl]-3(S)-methoxymethyl-β-alanine

IR (KBr pellet) : 3074, 2935, 2862, 1624 cm^{-1}

NMR (D_2O, δ) : 1.31-1.86 (9H, m), 1.93-2.05 (3H, m), 2.26-2.54 (5H, m), 2.76-3.05 (3H, m), 3.15-3.50 (2H, m), 3.37 (3H, s), 3.48 (2H, d, J=6.3Hz), 3.79-3.97 (1H, m), 4.15-4.44 (2H, m)

MASS (m/z) : 384 (M^++1)

Example 140

N-[(R)-1-[3-(4-Piperidyl)propanoyl]-3-piperidylcarbonyl]-2-benzoylaminomethyl-β-alanine

IR (KBr pellet) : 3381, 3311, 3064, 2937, 2862, 1643 cm^{-1}

NMR (D_2O, δ) : 1.27-1.99 (12H, m), 2.35-2.57 (3H, m), 2.72-3.08 (4H, m), 3.13-3.49 (5H, m), 3.56 (2H, d, J=6.7Hz), 3.80-4.31 (3H, m), 7.50-7.63 (3H, m), 7.75-7.79 (2H, m)

MASS (m/z) : 473 (M^++1)

Example 141

N-[(R)-1-[3-(4-Piperidyl)propanoyl]-3-piperidylcarbonyl]-2-acetylaminomethyl-β-alanine

IR (KBr pellet) : 3444, 3086, 2939, 2862, 1647 cm^{-1}

NMR (D_2O, δ) : 1.30-1.94 (11H, m), 2.06 (3H, s), 2.36-2.70 (4H, m), 2.77-3.04 (3H, m), 3.13-3.45 (7H, m), 3.83-4.00 (2H, m), 4.15-4.38 (2H, m)

MASS (m/z) : 411 (M^++1)

Example 142

N-[(R)-1-[3-(4-Piperidyl)propanoyl]-3-piperidylcarbonyl]-3,3-dimethyl-β-alanine

NMR (D_2O, δ) : 1.25-1.90 (8H, m), 1.39 (6H, s), 1.90-2.10 (3H, m), 2.20-2.65 (5H, m), 2.70-3.10 (3H, m), 3.10-3.55 (3H, m), 3.70-4.05 (1H, m), 4.15-4.40 (1H, m)

MASS (m/z) : 368 (M^++1)

Example 143

N-[(R)-1-[3-(1,2,3,6-Tetrahydro-4-pyridyl)propanoyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester

NMR (D_2O, δ) : 1.24 (3H, t, J=7.1Hz), 1.55-1.94 (5H, m), 2.24-2.65 (5H, m), 2.74 (1H, d, J=2.4Hz), 2.80-3.00 (6H, m), 3.30-3.42 (3H, m), 3.64 (1H, br), 3.83-3.90 (1H, m), 4.12-4.28 (1H, m), 4.17 (2H, q, J=7.1Hz), 5.48 (1H, br)

MASS (m/z) : 390 (M^++1)

Example 144

To a solution of N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine n-pentyl ester (0.65 g) in ethyl acetate (6 ml) was added 4N HCl in 1,4-dioxane (3.06 ml) at 0°C, and the reaction mixture was stirred for 2 hours at room temperature. The precipitates were filtered, washed with ether and dissolved in water, neutralized with saturated aqueous $NaHCO_3$, desalted by using the resin of HP-20 eluting with isopropanol:H_2O = (1:1), and 1N aqueous HCl was added, then freeze-dried to give N-[(R)-1-[3-(4-piperidyl)-(E)-acryloyl]-3(R)-piperidylcarbonyl]-3(S)-

ethynyl-β-alanine n-pentyl ester hydrochloride (184 mg, 32.2%).

IR (KBr pellet) : 3417, 3294, 3035, 2958, 2939, 2864, 2727, 1734, 1655 cm^{-1}

NMR (D_2O, δ) : 0.76-0.83 (3H, m), 1.18-1.32 (4H, m), 1.39-1.76 (7H, m), 1.88-2.00 (3H, m), 2.31-2.58 (2H, m), 2.67 (1H, d, J=2.4Hz), 2.75-3.20 (4H, m), 3.29-3.42 (3H, m), 3.80-4.27 (2H, m), 4.07 (2H, d, J=6.5Hz), 4.55-4.93 (2H, m), 6.38 (1H, d, J=15.2Hz), 6.51-6.63 (1H, m)

MASS (m/z) : 432 (M^+free+1)

The following compound was obtained according to a similar manner to that of Example 144.

Example 145

N-[(R)-1-[3-(4-Piperidyl)propanoyl]-3-piperidylcarbonyl]-2(S)-acetylamino-β-alanine n-pentyl ester hydrochloride

IR (KBr pellet) : 3439, 3390, 3359, 3064, 2956, 2941, 2864, 2731, 1738, 1653, 1622 cm^{-1}

NMR (D_2O, δ) : 0.85-0.93 (3H, m), 1.30-1.38 (3H, m), 1.43-1.88 (9H, m), 1.95-2.05 (6H, m), 2.34-2.54 (2H, m), 2.85-3.08 (2H, m), 3.14-3.46 (8H, m), 4.10-4.38 (2H, m), 4.54-5.01 (7H, m)

MASS (m/z) : 467 (M^+free+1)

Example 146

A mixture of N-[(R)-1-[3-(1-benzyloxycarbonyl-4-piperidyl)propanoyl]-3-piperidylcarbonyl]-2(S)-acetylamino-β-alanine (0.5 g) 1N HCl (0.94 ml) and 10% Pd-C (0.1 g) in tetrahydrofuran (5 ml) was hydrogenated at atmospheric pressure for 2 hours. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo. The residue was resolved in water, and neutralized

with saturated aqueous $NaHCO_3$, desalted by using the resin of HP-20 eluting with isopropanol:H_2O = (1:1), then freeze-dried to give N-[(R)-1-[3-(4-piperidyl)propanoyl-3-piperidylcarbonyl]-2(S)-acetylamino-β-alanine (0.34 g, 91.0%).

IR (KBr pellet) : 2943, 2862, 1608 cm^{-1}

NMR (D_2O, δ) : 1.31-1.88 (8H, m), 1.94-2.03 (4H, m), 2.03 (3H, s), 2.39-2.54 (3H, m), 2.80-3.05 (3H, m), 3.19-3.48 (5H, m), 3.63-3.74 (1H, m), 3.81-3.95 (1H, m), 4.18-4.34 (1H, m), 4.35-4.41 (1H, m)

Elemental Analysis Calcd. for $C_{19}H_{32}N_4O_5 \cdot 1.6H_2O$:
C 53.66, H 8.34, N 13.17
Found : C 53.63, H 8.56, N 13.03

The following compounds [Examples 147 to 148] were obtained according to a similar manner to that of Example 146.

Example 147

N-[(R)-1-[3-(4-Piperidyl)propanoyl]-3-piperidylcarbonyl]-2(S)-benzoylamino-β-alanine

IR (KBr pellet) : 2943, 2862, 1643 cm^{-1}

NMR (DMSO-d, δ) : 1.20-1.96 (13H, m), 2.22-2.45 (3H, m), 2.70-3.02 (3H, m), 3.08-3.27 (1H, m), 3.35-3.46 (2H, m), 3.58-3.80 (3H, m), 4.13-4.19 (1H, m), 4.57-4.70 (1H, m), 7.51-7.70 (3H, m), 7.78-7.86 (2H, m)

Elemental Analysis Calcd. for $C_{24}H_{34}N_4O_5 \cdot 1.1H_2O$:
C 60.26, H 7.63, N 11.71
Found : C 60.22, H 7.64, N 11.65

Example 148

N-[(R)-1-[3-(4-Piperidyl)propanoyl]-3-piperidylcarbonyl]-2(S)-(4-methoxybenzoylamino)-β-alanine

IR (KBr pellet) : 2943, 2860, 1632, 1608 cm^{-1}

NMR ($DMSO_6$, δ) : 1.19-1.59 (7H, m), 1.65-2.00 (6H, m), 2.20-2.29 (1H, m), 2.37-2.45 (2H, m), 2.71-3.04 (3H, m), 3.12-3.25 (1H, m), 3.35-3.49 (2H, m), 3.60-3.82 (3H, m), 3.89 (3H, s), 4.08-4.20 (1H, m), 4.55-4.66 (1H, m), 7.09 (2H, dd, J=8.9 and 2.9Hz), 7.80 (2H, dd, J=8.8 and 1.9Hz)

Elemental Analysis Calcd. for $C_{25}H_{36}N_4O_6 \cdot 1.4H_2O$:

C 58.44, H 7.61, N 10.90

Found : C 58.43, H 7.73, N 10.85

Example 149

A solution of 3-[(R)-1-[3-(4-piperidyl)propanoyl]-3-piperidylcarbonyl]aminobenzoic acid hydrochloride (1 g) was neutralized by saturated aqueous $NaHCO_3$, desalted by using the resin of HP-20 eluting with H_2O:isopropanol = (1:1), then freeze-dried to give 3-[(R)-1-[3-(4-piperidyl)propanoyl]-3-piperidylcarbonyl]aminobenzoic acid (732 mg 80.1%).

IR (KBr pellet) : 2860, 1678, 1616 cm^{-1}

NMR (D_2O, δ) : 1.20-1.69 (6H, m), 1.77-2.09 (5H, m), 2.32-2.50 (2H, m), 2.56-2.94 (3H, m), 3.14-3.38 (4H, m), 3.53-3.93 (2H, m), 4.16-4.23 (1H, m), 7.47 (1H, t, J=7.8Hz), 7.62-7.72 (2H, m), 7.84-7.87 (1H, m)

MASS (m/z) : 388 (M^++1)

$[\alpha]_D^{25}$ = -18.63° (C=1.0, MeOH)

Elemental Analysis Calcd. for $C_{21}H_{29}N_3O_4 \cdot 1.7H_2O$:

C 60.33, H 7.81, N 10.05

Found : C 60.42, H 8.35, N 9.97

The following compounds [Examples 150 to 152] were obtained according to a similar manner to that of Example 149.

Example 150

3-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]aminobenzoic acid

IR (KBr pellet) : 2860, 1676, 1655, 1608 cm^{-1}

NMR (D_2O, δ) : 1.35-1.96 (8H, m), 2.26-2.76 (3H, m), 2.87-3.21 (3H, m), 3.28-3.53 (2H, m), 3.68-3.98, 4.38-4.44 (total 3H, m), 6.41 (1H, dd, J=15.4 and 4.8Hz), 6.60 (1H, td, J=15.4 and 6.1Hz), 7.46 (1H, t, J=7.9Hz), 7.62-7.71 (2H, m), 7.77-7.84 (1H, m)

MASS (m/z) : 386 (M^++1)

$[\alpha]_D^{25}$ = -19.97° (C=1.0, MeOH)

Elemental Analysis Calcd. for $C_{21}H_{27}N_3O_4 \cdot 1.9H_2O$:

C 60.10, H 7.40, N 10.01

Found : C 60.05, H 7.73, N 9.85

Example 151

4-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]aminobenzoic acid

IR (Nujol) : 1660, 1650, 1600 cm^{-1}

NMR (D_2O, δ) : 1.36-1.74 (4H, m), 1.83-2.09 (4H, m), 2.19-2.34 (1H, m), 2.50-2.70 (1H, m), 2.77-3.49 (6H, m), 3.59-3.68 (1H, m), 3.81-4.00 (2H, m), 6.44-6.60 (2H, m), 7.51 (2H, d, J=8.5Hz), 7.88 (2H, d, J=8.6Hz)

MASS (m/z) : 386 (M^++1)

$[\alpha]_D^{25}$ = -46.0° (C=0.2, MeOH)

Elemental Analysis Calcd. for $C_{21}H_{27}N_3O_4 \cdot 2.4H_2O$:

C 58.84, H 7.48, N 9.80

Found : C 58.90, H 7.66, N 9.61

Example 152

4-[(R)-1-[3-(4-Piperidyl)propanoyl]-3-piperidylcarbonyl]aminobenzoic acid

IR (KBr pellet) : 3477, 3051, 2943, 2862, 1680,

1624, 1603 cm^{-1}

NMR (D_2O, δ) : 1.27-1.73 (6H, m), 1.81-2.10 (5H, m), 2.45-2.54 (2H, m), 2.72-2.93 (3H, m), 3.29-3.54 (4H, m), 3.69-4.20 (3H, m), 7.54 (2H, d, J=8.6Hz), 7.89 (2H, d, J=8.6Hz)

MASS (m/z) : 388 (M^++1)

$[\alpha]_D^{25}$ = -28.8° (C=1.0, MeOH)

Elemental Analysis Calcd. for $C_{21}H_{29}N_3O_4 \cdot 2.1H_2O$:
C 59.31, H 7.87, N 9.88

Found : C 59.21, H 8.20, N 9.72

Example 153

To a solution of N-[(R)-1-[3-(4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2(S)-trifluoroacetylamino-β-alanine trifluoroacetate in water (4 ml) was added Pd/C (10% dry, 16 mg) and the mixture was stirred at room temperature under hydrogen at atmospheric pressure for 4 hours. Catalyst was filtered off and filtrate was evaporated in vacuo to give N-[(R)-1-[3-(4-piperidyl)propanoyl]-3-piperidylcarbonyl]-2(S)-trifluoroacetylamino-β-alanine trifluoroacetate as a colorless oil (45 mg, 54.9%).

IR (Neat) : 1720 cm^{-1}

NMR (D_2O, δ) : 1.20-2.15 (11H, m), 2.35-2.65 (3H, m), 2.45-3.10 (3H, m), 3.05-3.30 (1H, m), 3.30-3.50 (2H, m), 3.60-4.00 (3H, m), 4.05-4.40 (1H, m), 4.50-4.70 (1H, m)

The following compounds [Examples 154 to 155] were obtained according to a similar manner to that of Example 153.

Example 154

N-[(R)-1-[3-(4-Piperidyl)propanoyl]-2(S)-[4-trifluoromethyl)benzoylamino]-β-alanine

IR (Nujol) : 1610 cm^{-1}

NMR (D_2O, δ) : 1.20-2.10 (11H, m), 2.20-2.60 (3H, m), 2.65-3.55 (6H, m), 3.55-3.95 (3H, m), 4.00-4.25 (1H, m), 4.50-4.75 (2H, m), 7.84-7.97 (4H, m)

MASS (m/z) : 527 (M^++1)

Example 155

N-[(R)-1-[3-(4-Piperidyl)propanoyl]-3-piperidylcarbonyl]-3(S)-trifluoroacetylaminomethyl)-β-alanine trifluoroacetate

IR (Nujol) : 1710 cm^{-1}

NMR (D_2O, δ) : 1.20-2.05 (12H, m), 2.25-2.85 (6H, m), 2.85-3.10 (3H, m), 3.10-3.55 (5H, m), 3.70-3.95 (1H, m), 4.05-4.30 (1H, m), 4.30-4.60 (1H, m)

MASS (m/z) : 465 (M^++1)

Example 156

To a stirred solution of N-[(R)-1-[3-(4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2(S)-trifluoroacetylamino-β-alanine ethyl ester (334 mg, 0.58 mmol) in ethyl acetate (1.5 ml) was added a solution of 4N-hydrogen chloride in ethyl acetate (1.0 ml, 4 mmol). After the solution was stirred for 2 hours at ambient temperature, the solvent was evaporated in vacuo. The residue was dissolved in 0.1M phosphate buffer (pH=7.3, 200 ml). To the solution was added Porcine liver esterase (0.5 ml), and the solution was stirred for 7 days at ambient temperature. Solvent was evaporated, and the residue was purified by HPLC to give N-[(R)-1-[3-(4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2(S)-trifluoroacetylamino-β-alanine trifluoroacetate as a colorless oil (220 mg, 67.5%).

IR : 1720 cm^{-1}

NMR (D_2O, δ) : 1.35-1.90 (5H, m), 1.90-2.15 (3H, m), 2.35-2.70 (2H, m), 2.80-3.15 (3H, m), 3.15-3.40 (1H, m), 3.40-3.55 (2H, m), 3.60-4.05 (4H, m), 4.05-4.45 (1H, m), 6.49 (1H, d, J=15.6Hz), 6.55-6.75 (1H, m)

The following compounds [Examples 157 to 158] were obtained according to a similar manner to that of Example 156.

Example 157

N-[(R)-1-[3-(3-Azetidinyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine trifluoroacetate

IR (Nujol) : 1650 cm^{-1}

NMR (D_2O, δ) : 1.35-1.65 (1H, m), 1.65-1.90 (2H, m), 1.90-2.15 (1H, m), 2.35-2.60 (1H, m), 2.73 (1H, d, J=2.5Hz), 2.75-2.95 (2H, m), 2.95-3.50 (2H, m), 3.70-4.00 (2H, m), 4.00-4.40 (5H, m), 4.85-5.15 (1H, m), 6.54 (1H, d, J=15.4Hz), 6.79 (1H, dd, J=15.4 and 7.4Hz)

MASS (m/z) : 334 (M^++1)

Example 158

N-[(R)-1-[4-(3-Azetidinyl)-(E)-2-butenoyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine trifluoroacetate

IR (Neat) : 1720 cm^{-1}

NMR (D_2O, δ) : 1.35-2.10 (5H, m), 2.30-2.55 (1H, m), 2.59 (2H, t, J=6.8Hz), 2.73 (1H, d, J=2.3Hz), 2.75-3.50 (5H, m), 3.80-4.35 (6H, m), 4.85-5.00 (1H, m), 6.42-6.65 (2H, m)

MASS (m/z) : 348 (M^++1)

Example 159

To a solution of N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine pivaloyloxymethyl ester (0.39 g) in ethyl acetate (4 ml) was added 4N HCl in ethyl acetate (1.61 ml) at 0°C, and the reaction mixture was stirred for 3 hours at room temperature. The precipitates were filtered and washed with diethyl ether, and dissolved with water. The solution was purified by HPLC eluting with 0.1% aqueous trifluoroacetic acid:CH_3CN = (67:33) to give N-[(R)-1-[3-(4-piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine pivaloyloxymethyl ester trifluoroacetate (301.4 mg, 81.2%).

IR (KBr pellet) : 3373, 3049, 2981, 2943, 2870, 2536, 1757, 1674, 1659, 1601 cm^{-1}

NMR (D_2O, δ) : 1.19 (9H, s), 1.46-1.86 (6H, m), 1.93-2.11 (3H, m), 2.39-2.66 (2H, m), 2.77 (1H, d, J=2.4Hz), 2.90-2.95 (2H, m), 3.00-3.30 (4H, m), 3.40-3.52 (3H, m), 3.90-4.13 (2H, m), 5.78 (2H, s), 6.45 (1H, d, J=15.7Hz), 6.64 (1H, dd, J=15.5 and 6.2Hz)

MASS (m/z) : 476 (M^+free+1)

The following compounds [Examples 160 to 161] were obtained according to a similar manner to that of Example 159.

Example 160

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-β-alanine pivaloyloxymetyl ester trifluoroacetate

IR (KBr pellet) : 3325, 2978, 2870, 2750, 1757, 1657, 1603 cm^{-1}

NMR (D_2O, δ) : 1.19 (9H, s), 1.40-2.12 (10H, m), 2.37-2.59 (2H, m), 2.66 (2H, t, J=6.4Hz), 2.95-3.34 (3H, m), 3.43-3.52 (4H, m), 3.92-4.35 (2H, m), 5.76 (2H, s), 6.46 (1H, d, J=15.5Hz), 6.64

(1H, dd, J=15.5 and 6.2Hz)

MASS (m/z) : 452 (M^+free+1)

Example 161

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-trifluoroacetylaminomethyl-β-alanine trifluoroacetate

IR (Nujol) : 1720, 1650 cm^{-1}

NMR (D_2O, δ) : 1.35-2.15 (9H, m), 2.30-2.80 (4H, m), 2.80-3.60 (9H, m), 3.75-4.05 (1H, m), 4.05-4.25 (1H, m), 4.35-4.60 (1H, m), 6.43 (1H, d, J=14.9Hz), 6.55-6.70 (1H, m)

MASS (m/z) : 463 (M^++1)

Example 162

1N aqueous LiOH (3.0 ml) was added to a solution of N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)-(Z)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester (1.0 g) in tetrahydrofuran (5 ml)-EtOH (5 ml) at 0°C. The reaction mixture was stirred for 2 hours at room temperature, then water was added, and the whole was washed with diethyl ether. The aqueous layer was made acidic with 20% aqueous $KHSO_4$, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, evaporated in vacuo. The residue was dissolved in ethyl acetate (10 ml) and 4N HCl in ethyl acetate (5.1 ml) was added. The reaction mixture was stirred for 2 hours and diethyl ether was added. The precipitates were collected with filtration and dissolved with water. The solution was neutralized with saturated aqueous $NaHCO_3$ and purified by HP-20 resin eluting with isopropanol/water= (0-30%) to give N-[(R)-1-[3-(4-piperidyl)-(Z)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine (0.5 g, 67.8%)

NMR (D_2O, δ) : 1.10-1.58 (8H, m), 2.06-2.32 (5H, m), 2.58-2.75 (2H, m), 2.80-2.89 (1H, m), 3.00-3.11 (2H, m), 3.40-3.55 (1H, m), 3.73-3.86 (1H, m), 4.45-4.52 (2H, m), 5.39-5.52 (1H, m), 5.77 (1H, dd, J=2.4 and 11.6Hz)

MASS (m/z) : 362 (M^++1)

The following compounds [Examples 163 to 164] were obtained according to a similar manner to that of Example 162.

Example 163

N-[(R)-1-[1,2,3,4-Tetrahydroisoquinolin-6-yl)-carbonyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine

IR (Nujol) : 1660 cm^{-1}

NMR (D_2O, δ) : 1.40-2.35 (5H, m), 2.35-2.80 (1H, m), 2.45 (1H, dd, J=7.0 and 4.1Hz), 2.64 (1H, d, J=7.6Hz), 3.05-3.50 (2H, m), 3.17 (2H, t-like), 3.50-3.85 (2H, m), 3.56 (2H, t, J=6.2Hz), 7.20-7.50 (3H, m)

MASS (m/z) : 384 (M^++1)

Example 164

N-[(R)-1-[1,2,3,6-Tetrahydro-4-pyridyl)propanoyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine hydrochloride

NMR (D_2O, δ) : 1.51-1.96 (5H, m), 2.26-2.50 (5H, m), 2.60-2.68 (6H, m), 2.86-3.07 (1H, m), 3.18-3.44 (3H, m), 3.65 (1H, br), 3.83-3.95 (1H, m), 4.09-4.30 (1H, m), 5.49 (1H, br)

MASS (m/z) : 362 (M^++1)

Example 165

1N aqueous LiOH (0.9 ml) was added to a solution of N-[(R)-1-[3-(1-tert-butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester (0.33 g) in tetrahydrofuran (1.5 ml)-EtOH (1.5 ml) at 0°C. The reaction mixture was

stirred for 2 hours at room temperature, then water was added, and the whole was washed with diethyl ether. The aqueous layer was made acidic with 20% aqueous $KHSO_4$, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was dissolved in ethyl acetate (5 ml) and 4N HCl in ethyl acetate (2.5 ml) was added. The reaction mixture was stirred for 2 hours and diethyl ether was added. The precipitates were collected with filtration and washed with diethyl ether to give N-[(R)-1-[3-(1,2,3,6-tetrahydro-4-pyridyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine hydrochloride (0.12 g, 44.6%).

NMR (D_2O, δ) : 1.20-1.38 (2H, m), 1.40-1.78 (4H, m), 2.20-2.35 (3H, m), 2.43 (1H, d, J=2Hz), 2.55-2.60 (3H, m), 2.75-3.14 (4H, m), 3.56-3.75 (2H, m), 3.90-4.02 (1H, m), 5.86 (1H, br), 6.23 (1H, d, J=15Hz), 6.88 (1H, dd, J=2 and 15Hz)

MASS (m/z) : 360 (M^+free+1)

The following compounds [Examples 166 to 169] were obtained according to a similar manner to that of Example 165.

Example 166

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-(3-methyl-5-isoxazolyl)-β-alanine hydrochloride

NMR (D_2O, δ) : 1.55-1.79 (5H, m), 1.92-2.09 (4H, m), 2.26 (3H, s), 2.56-2.60 (2H, m), 2.93-3.29 (5H, m), 3.44-3.50 (2H, m), 3.93-4.27 (2H, m), 5.42-5.48 (1H, m), 6.25 (1H, s), 6.45 (1H, d, J=15.5Hz), 6.57-6.72 (1H, m)

MASS (m/z) : 419 (M^+)

Example 167

N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-2(S)-[4-(trifluoromethyl)benzoylamino]-β-alanine

IR (Nujol) : 1740, 1680 cm^{-1}

NMR (D_2O, δ) : 1.20-1.85 (5H, m), 1.85-2.15 (3H, m), 2.35-2.65 (2H, m), 2.85-3.35 (6H, m), 3.35-4.00 (3H, m), 4.00-4.40 (1H, m), 4.55-4.70 (2H, m), 6.35 (1H, dd, J=19.0 and 16.0Hz), 6.50-6.66 (1H, m), 7.85 (2H, d, J=9.0Hz), 7.93 (2H, d, J=9.0Hz)

MASS (m/z) : 525 (M^++1)

Example 168

N-[(R)-1-[4-(3-Piperidyl)-(E)-2-butenoyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine

NMR (D_2O, δ) : 1.10-2.10 (8H, m), 2.28 (1H, t, J=6.8Hz), 2.35-3.55 (10H, m), 2.67 (1H, d, J=2.3Hz), 2.65-4.40 (2H, m), 4.70-4.95 (2H, m), 6.40-6.55 (1H, m), 6.58-6.65 (1H, m)

MASS (m/z) : 476 (M^++1)

Example 169

N-[(R)-1-[3-(1,2,3,6-Tetrahydro-4-pyridyl)propanoyl]-3-piperidylcarbonyl]-3(S)-(3-methyl-5-isoxazolyl)-β-alanine hydrochloride

NMR (D_2O, δ) : 1.28-1.66 (5H, m), 2.06 (3H, s), 2.06-2.09 (4H, m), 2.19-2.39 (3H, m), 2.62-2.84 (5H, m), 3.04-3.10 (3H, m), 3.37 (2H, br), 5.17-5.24 (1H, m), 5.99 (1H, br)

MASS (m/z) : 419 (M^++1)

Example 170

LiOH (40 mg, 1.66 mmol) was added to a solution of N-[(R)-1-[4-(1-tert-butoxycarbonyl-3-azetidinyl)butanoyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine ethyl ester (663

mg, 1.39 mmol) in tetrahydrofuran (6.0 ml)-EtOH (6.0 ml)-H_2O (6.0 ml). The reaction mixture was stirred for 2 hours at room temperature. Solvent was evaporated in vacuo, then water was added, and the whole was washed with diethyl ether. The aqueous layer was made acidic with 5% aqueous $KHSO_4$, and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated in vacuo. Trifluoroacetic acid (2 ml) was added to the residue. The reaction mixture was stirred for 1 hour at room temperature. Solvent was evaporated in vacuo. The residue was purified by HPLC eluting with 0.1% aqueous trifluoroacetic acid:CH_3CN = (14:86) to give N-[(R)-1-[4-(3-azetidinyl)butanoyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine trifluoroacetate (250mg, 38.8%).

IR (Neat) : 1720, 1640 cm^{-1}

NMR (D_2O, δ) : 1.30-2.15 (8H, m), 2.25-2.60 (3H, m), 2.73 (1H, d, J=2.3Hz), 2.90-3.45 (5H, m), 3.65-3.95 (3H, m), 4.00-4.30 (3H, m)

MASS (m/z) : 350 (M^++1)

Example 171

Trifluoroacetic acid (3 ml) was added to N-[(R)-1-[3-(1-tert-butoxycarbonyl-3-azetidinyl)propanoyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine (1.11 g, 2.55 mmol). The reaction mixture was stirred for 1 hour at room temperature. Solvent was evaporated in vacuo. The residue was purified by HPLC to give N-[(R)-1-[3-(3-azetidinyl)propanoyl]-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine trifluoroacetate (270mg, 23.6%).

IR (Nujol) : 1650 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-2.15 (7H, m), 2.20-2.60 (3H, m), 2.73 (1H, d, J=2.3Hz), 2.80-3.50 (6H, m), 3.65-3.95 (3H, m), 3.95-4.35 (4H, m), 4.85-5.00 (1H, m)

MASS (m/z) : 336 (M^++1)

Example 172

Trifluoroacetic acid (3 ml) was added to N-[(R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)propanoyl]-3-piperidylcarbonyl]-3(S)-acetylaminomethyl-β-alanine tert-butyl ester. The solvent was evaporated in vacuo. The residue was neutralized with saturated aqueous $NaHCO_3$ and purified by HP-20 resin eluting with isopropanol/water (0-50% to give N-[(R)-1-[3-(4-piperidyl)propanoyl]-3-piperidylcarbonyl]-3(S)-acetylaminomethyl-β-alanine (120mg, 50.0%).

IR (Nujol) : 1640, 1600 cm^{-1}

NMR (D_2O, δ) : 1.20-1.70 (8H, m), 1.70-2.15 (7H, m), 1.98 (3H, s), 2.40-2.65 (3H, m), 2.65-3.10 (2H, m), 3.10-3.50 (6H, m), 3.70-4.05 (1H, m), 4.05-4.25 (2H, m)

MASS (m/z) : 411 (M^++1)

The following compound was obtained according to a similar manner to that of Example 172.

Example 173

N-[(R)-1-[3-(4-Piperidyl)propanoyl]-3-piperidylcarbonyl]-3(S)-benzoylaminomethyl-β-alanine.

IR (Nujol) : 1620 cm^{-1}

NMR (D_2O, δ) : 1.35-2.35 (13H, m), 2.35-2.65 (3H, m), 2.70-3.05 (2H, m), 2.10-3.65 (5H, m), 3.65-4.25 (2H, m), 4.25-4.40 (1H, m), 7.49-7.62 (3H, m), 7.75-7.79 (2H, m)

MASS (m/z) : 473 (M^++1)

The following compound was obtained according to a similar manner to that of Example 35.

Example 174

N-[[2-[3-(1-tert-Butoxycarbonyl-4-piperidyl)-(E)-

acryloyl]-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl-3(S)-ethynyl-β-alanine ethyl ester

MASS (m/z) : 538 (M^++1)

The following compound was obtained according to a similar manner to that of Example 170.

Example 175

N-[[2-[3-(4-Piperidyl)-(E)-acryloyl]-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]-3(S)-ethynyl-β-alanine trifluoroacetate

IR (Neat) : 1740 cm^{-1}

NMR (D_2O, δ) : 1.50-1.80 (2H, m), 2.00-2.20 (2H, m), 2.45-2.90 (4H, m), 3.00-3.25 (2H, t-like), 3.35-3.55 (2H, m), 3.65-3.85 (1H, m), 3.85-4.00 (1H, m), 4.30-4.65 (1H, m), 4.65-5.30 (3H, m), 6.40-6.55 (1H, m), 6.65-6.80 (1H, m), 7.20-7.45 (4H, m)

MASS (m/z) : 410 (M^++1)

The following compound was obtained according to a similar manner to that of Examples 35, 75 and 110.

Example 176

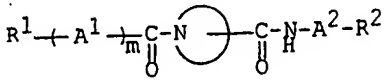
N-[(R)-1-[3-(4-Piperidyl)-(E)-acryloyl]-3-piperidylcarbonyl]-3(S)-(2H-1,2,3-triazol-4-yl)-β-alanine trifluoroacetate

NMR (D_2O, δ) : 1.56-2.07 (9H, m), 2.50-2.64 (2H, m), 3.02-3.50 (7H, s), 3.85-4.27 (2H, m), 5.53-5.57 (1H, m), 6.45 (1H, d, J=15.5Hz), 6.56-6.63 (1H, m), 7.86 (1H, d, J=5.0Hz)

MASS (m/z) : 405 (M^++1)

C L A I M S

1. A compound of the formula :



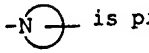
wherein

R^1 is piperidyl, piperidyl having amino protective group, tetrahydropyridyl, tetrahydropyridyl having amino protective group, azetidinyl, azetidinyl having amino protective group, tetrahydroisoquinolyl or tetrahydroisoquinolyl having amino protective group,

R^2 is carboxy or protected carboxy,

A^1 is lower alkylene, lower alkanyl-ylidene, lower alkenylene, cyclo(lower)alkylene or arylene,

A^2 is lower alkylene which may have one or more suitable substituent(s) or arylene,

 is piperidinediyl or

tetrahydroisoquinolinediyl, and

m is an integer of 0 or 1,

with proviso that

when R^1 is piperidyl,

A^1 is lower alkylene, and

A^2 is lower alkylene which may have one or more suitable substituent(s) except 5 or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), which may have one or more lower alkyl; ar(lower)alkoxy(lower)alkyl; hydroxy(lower)alkyl;

lower alkoxy(lower)alkyl; cyclo(lower)alkyl; aroylamino(lower)alkyl; lower alkanoylamino-(lower)alkyl which may have halogen; lower alkanoylamino having halogen; and aroylamino having halo(lower)alkyl;

then R^2 is pentyloxycarbonyl, isopentyloxycarbonyl, isohexyloxycarbonyl, phenethyloxycarbonyl, aryloxycarbonyl or indanyloxycarbonyl,

or a salt thereof.

2. A compound of claim 1, wherein

A^2 is lower alkylene which may have one or more suitable substituent(s) selected from the group consisting of lower alkyl; lower alkynyl; aryl; ar(lower)alkyl which may have one or more lower alkoxy; lower alkanoylamino which may have one or more halogen; aroylamino which may have one or more suitable substituent(s) selected from the group consisting of lower alkoxy and halo(lower)alkyl; 5 or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have lower alkyl; 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s); lower alkoxy(lower)alkyl; cyclo(lower)alkyl; hydroxy(lower)alkyl; ar(lower)alkoxy(lower)alkyl; lower alkanoylamino-(lower)alkyl which may have one or more halogen and aroylamino(lower)alkyl, or arylene.

3. A compound of claim 2, wherein

A^1 is lower alkenylene,

A^2 is lower alkylene which may have 1 to 3 suitable substituent(s) selected from the group consisting of lower alkyl, lower alkynyl, aryl, ar(lower)alkyl which may have 1 to 3 lower alkoxy, lower

alkanoylamino which may have 1 to 3 halogen, aroylamino which may have 1 to 3 halo(lower)alkyl, heterocyclic group which may have 1 to 3 lower alkyl, lower alkoxy(lower)alkyl, cyclo(lower)alkyl, hydroxy(lower)alkyl, ar(lower)alkoxy(lower)alkyl and lower alkanoylamino(lower)alkyl which may have 1 to 3 halogen, or arylene,

 is piperidinediyl or tetrahydroisoquinolinediyl,

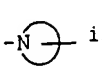
and

m is an integer of 1.

4. A compound of claim 3, wherein

R^1 is piperidyl, piperidyl having amino protective group, tetrahydropyridyl, tetrahydropyridyl having amino protective group, azetidinyl, azetidinyl having amino protective group, tetrahydroisoquinolyl or tetrahydroisoquinolyl having amino protective group,

A^2 is lower alkylene, lower alkylene which has one suitable substituent selected from the group consisting of lower alkyl, lower alkynyl, aryl, ar(lower)alkyl which may have 1 or 2 lower alkoxy, lower alkanoylamino which may have 3 halogens, aroylamino which may have one tri-halo(lower)alkyl, 5 or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have one lower alkyl, 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), lower alkoxy(lower)alkyl, cyclo(lower)alkyl, hydroxy(lower)alkyl, ar(lower)alkoxy(lower)alkyl and lower alkanoylamino(lower)alkyl which may have 3 halogens, or phenylene,

 is piperidinediyl or tetrahydroisoquinolinediyl.

5. A compound of claim 4, wherein
R^1 is piperidyl or tetrahydropyridyl,
A^2 is lower alkylene or lower alkylene which has one suitable substituent selected from the group consisting of lower alkyl, lower alkynyl, phenyl, phenyl(lower)alkyl which may have 1 or 2 lower alkoxy, lower alkanoylamino, benzoylamino which may have one tri-halo(lower)alkyl, isoxazolyl which has one lower alkyl, triazolyl and phenyl(lower)alkoxy(lower)alkyl,

 is piperidinediyl.

6. A compound of claim 2, wherein
R^1 is piperidyl,
R^2 is pentyloxycarbonyl, isopentyloxycarbonyl, isohexyloxycarbonyl, phenethyloxycarbonyl, phenyloxycarbonyl or indanyloxycarbonyl,
A^1 is lower alkylene,
A^2 is lower alkylene which has one substituent selected from the group consisting of lower alkynyl and lower alkanoylamino,

 is piperidinediyl, and

m is an integer of 1.

7. A compound of claim 2, wherein
R^1 is piperidyl or piperidyl having amino protective group,
A^1 is lower alkylene,
A^2 is lower alkylene which has one substituent selected

from the group consisting of 5 or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) having lower alkyl, phenyl(lower)alkoxy(lower)alkyl, hydroxy(lower)alkyl, lower alkoxy(lower)alkyl, cyclo(lower)alkyl, benzoylamino(lower)alkyl, lower alkanoylamino(lower)alkyl, tri-halo(lower)alkanoylamino, benzoylamino having tri-halo(lower)alkyl and tri-halo(lower)-alkanoylamino(lower)alkyl or phenylene,

 is piperidinediyl, and

m is an integer of 1.

8. A compound of claim 7, wherein
R^1 is piperidyl,
R^2 is carboxy,
A^1 is lower alkylene,
A^2 is lower alkylene which has one substituent selected from the group consisting of isoxazolyl having lower alkyl, tri-halo(lower)alkylbenzoylamino, benzoylamino(lower)alkyl, and tri-halo(lower)alkanoylamino(lower)alkyl.

9. A compound of claim 2, wherein
R^1 is tetrahydropyridyl or tetrahydropyridyl having amino protective group,
A^1 is lower alkylene,
A^2 is lower alkylene which has one substituent selected from the group consisting of lower alkynyl and 5 or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) having lower alkyl,

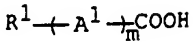
 is piperidinediyl, and

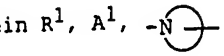
m is an integer of 1.

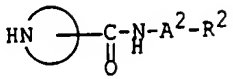
10. A compound of claim 9, wherein
R^1 is tetrahydropyridyl,
R^2 is carboxy,
A^1 is lower alkylene and
A^2 is lower alkylene which has one substituent selected from the group consisting of lower alkynyl and isoxazolyl having lower alkyl.

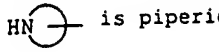
11. A process for preparing a compound of claim 1, or a salt thereof, which comprises

(i) reacting a compound of the formula :



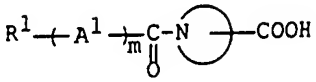
wherein R^1, A^1,  and m are each as defined in claim 1,
or its reactive derivative at the carboxy group
or a salt thereof, with a compound of the formula :



wherein R^2 and A^2 are each as defined in claim 1, and
 is piperidyl or tetrahydropyridyl,
or its reactive derivative at the amino group

or a salt thereof,

(ii) reacting a compound of the formula :

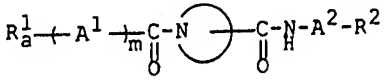


wherein R^1, A^1, and m are each as defined in claim 1,
or its reactive derivative at the carboxy group
or a salt thereof, with a compound of the formula :

$$H_2N\text{-}A^2\text{-}R^2$$

wherein R^2 and A^2 are each as defined in claim 1,
or its reactive derivative at the amino group
or a salt thereof, or

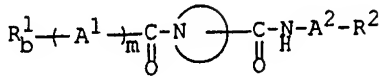
(iii) subjecting a compound of the formula :



wherein R^2, A^1, A^2, and m are each as defined in claim 1, and
R^1_a is piperidyl having amino protective group, tetrahydropyridyl having amino protective group, azetidinyl having amino protective group or tetrahydroisoquinolyl having

amino protective group,

or a salt thereof, to elimination reaction of the amino protective group, to give a compound of the formula :



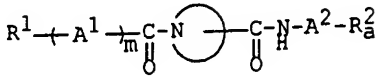
wherein R^2, A^1, A^2,  and m are each as defined in

claim 1, and

R^1_b is piperidyl, tetrahydropyridyl, azetidinyl or tetrahydroisoquinolyl,

or a salt thereof, or

(iv) subjecting a compound of the formula :

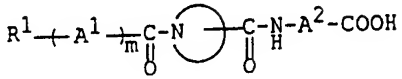


wherein R^1, A^1, A^2,  and m are each as defined in

claim 1, and

R^2_a is protected carboxy,

or a salt thereof, to elimination reaction of carboxy protective group, to give a compound of the formula :

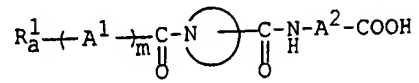


wherein R^1, A^1, A^2,  and m are each as defined

above,

or a salt thereof, or

(v) subjecting a compound of the formula :

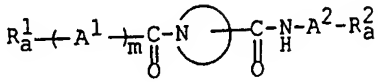


wherein R^1_a is as defined above, and

A^1, A^2, and m are each as defined in

claim 1,

or its reactive derivative at the carboxy group or a salt thereof, to protecting reaction of the carboxy, to give a compound of the formula :



wherein R^1_a and R^2_a are each as defined above, and

A^1, A^2, and m are each as defined in

claim 1,

or a salt thereof.

12. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers or excipients.

13. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament.

14. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

15. A method for the prevention and/or the treatment of diseases caused by thrombus formation; restenosis or reocclusion; the thrombus formation in case of vascular surgery, valve replacement, extracorporeal circulation or transplantation; disseminated intravascular coagulation; thrombotic thrombocytopenic; essential thrombocytosis; inflammation; immune diseases; or metastasis; or for the adjuvant therapy with thrombolytic drug or anticoagulant; which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

INTERNATIONAL SEARCH REPORT

International Application No
PC . JP 96/00643

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/36 C07D217/26 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,95 25091 (ORTHO PHARMACEUTICAL CORP., USA) 21 September 1995 see the whole document ---	1-15
P,X	WO,A,95 11228 (SUMITOMO PHARMACEUTICALS CO., LTD., JAPAN) 27 April 1995 see page 62 ---	1-15
P,X	WO,A,95 08536 (FUJISAWA PHARMACEUTICAL CO., LTD., JAPAN) 30 March 1995 see the whole document --- -/--	1-15

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 June 1996	28. 06. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl. Fax (+ 31-70) 340-3016	Kissler, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PC JP 96/00643

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	J. MED. CHEM. (1995), 38(10), 1582-92 CODEN: JMCMAR;ISSN: 0022-2623, 12 May 1995, XP002006052 HOEKSTRA, WILLIAM J. ET AL: "Design and Evaluation of Nonpeptide Fibrinogen.gamma. Chain-Based GPIIB/IIIA Antagonists" see the whole document ---	1-15
A	BIOORG. MED. CHEM. LETT. (1994), 4(11), 1361-4 CODEN: BMCLE8;ISSN: 0960-894X, 1994, XP002006053 HOEKSTRA, WILLIAM J. ET AL: "Adamantane and nipecotic acid derivatives as novel.beta.-turn mimics" see the whole document ---	1-15
X	EP,A,0 445 796 (HOFFMANN-LA ROCHE, F., A.-G., SWITZ.) 11 September 1991 see claim 1 see example 15 ---	1-15
A	WO,A,91 07976 (RORER INTERNATIONAL , INC., USA) 13 June 1991 see the whole document -----	1-15

Form PCT ISA 210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 96/00643

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 15 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

INTERNATIONAL SEARCH REPORT

..aformation on patent family members

Inter. nal Application No
PCT/JP 96/00643

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9525091	21-09-95	AU-B-	2119195	03-10-95
		CA-A-	2163027	21-09-95
		FI-A-	955498	15-01-96
		NO-A-	954609	05-01-96
WO-A-9511228	27-04-95	AU-B-	7862794	08-05-95
WO-A-9508536	30-03-95	AU-B-	7665794	10-04-95
		CN-A-	1116847	14-02-96
		EP-A-	0669912	06-09-95
		ZA-A-	9407350	10-05-95
		JP-A-	8053415	27-02-96
EP-A-0445796	11-09-91	CA-A-	2037153	10-09-91
		IL-A-	97401	15-03-95
		JP-A-	4217652	07-08-92
		US-A-	5430024	04-07-95
		US-A-	5273982	28-12-93
WO-A-9107976	13-06-91	US-A-	5053392	01-10-91
		AT-T-	135367	15-03-96
		AU-B-	636426	29-04-93
		AU-B-	6890091	26-06-91
		DE-D-	69025952	18-04-96
		EP-A-	0502926	16-09-92
		JP-T-	5504762	22-07-93